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SOME HISTORICAL ASPECTS OF THORACIC TRAUMA

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FROM the days of classical Greece until more modern times, the penetrating thoracic wound has been all too frequently synonymous with death, and its treatment has been the subject of great controversy. Such a lethal event is vividly described in Homer's *Iliad*[1]; when Idomeneus, king of Crete, slew Alcathous:

> . . . Idomeneus
> Speared him in midmost breast, and cleft the coat
> Of bronze about him; it had always kept
> Death off from him before, but now it rang
> Drily as it was split around the spear.
> Clanging he fell; the spear transfixed his heart,
> Which went on throbbing still, and shook the butt
> Till heavy Ares stopped it there at last.

Lacking in antiseptic or aseptic methods, deficient in knowledge of visceral anatomy, without replacement for shed blood, and restricted in anesthesia to vinous spirits and opium, surgical intervention among the ancients, in the case of thoracic wounds, was generally limited to a circumspect probing for foreign bodies, the extraction of impacted arrows and lance heads, and the application of occlusive dressings. On rare occasions, medieval surgeons were called upon to treat wounded patients in whom portions of prolapsed lung had become incarcerated between the adjacent ribs. As early as the thirteenth century, Rolando, a surgeon of Parma, recorded the treatment of a Bolognese youth 6 days after the latter had sustained a grievous wound of the chest. An extruding gangrenous segment of lung was excised, and the patient survived to accompany

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his master on a subsequent crusade to the Holy Land. This priority of Rolando is disputed by Theodoric in his *Chirurgia*,[2] in which he states that the operation was actually performed by Theodoric's father, Ugo de Lucca, with Rolando acting only as assistant. It is clear from this dispute that troubles with priority are not peculiar to modern times. Whatever the merits of this controversy it cannot be denied that two enquiring minds were at work during the early thirteenth century in the persons of Ugo de Lucca (who died in the year 1252) and his putative son, Friar Theodoric (1205-1298).

Ugo belonged to a well-known family, the Borgognoni, many of whom were men of medicine. He accompanied the Bolognese forces during a Crusade and, according to Castiglione,[3] was a most expert and courageous surgeon. He worked systematically to simplify the care of fresh wounds and fractures. Unfortunately he was not a writer, and his work has come down to us only in the *Chirurgia* of Theodoric, who was a Dominican monk and eventually Bishop of Cervia. These two, father and son, maintained that suppuration was not inevitable or even desirable in the healing process of wounds. They advocated gentle handling with cleansing irrigations of wine and water, and experimented with an anesthetic concoction composed of opium, mandragora, and other herbs. They were actually too far ahead of their time, and Theodoric's advices mouldered on library shelves for six hundred years. An excellent translation of the Latin manuscript has been provided by the late Eldridge Campbell of Albany.[2] To quote briefly from parts of the first and second books:

> *Chapt. 21.* If it [a wound] should be in the lung, the blood will come forth foaming, gasping occurs frequently, and the color of the patient fluctuates. . . . a chest wound has a double consideration, according to whether it occurs from an interior cause or from an exterior cause. . . . I mention the one from an exterior cause because if it should be fresh, it is possible for it to be consolidated and healed, and the application of medicine for cleansing the part is more effective. . .
>
> *Chapt. 22.* . . . It does not trouble me to write down at the end of this chapter certain empirical experiments, although they have not been tested by me, experiments which I know certain experienced men swear by. Therefore, for the purpose of drawing out an arrow, let there be said thrice on bended knee, the Lord's Prayer (that is, the Paternoster) and when these have been said, let the arrow be grasped with both hands joined as they are, and let be said 'Nicodemus drew out the nails from our Lord's hands and feet,' and [so] let this arrow be drawn out and it will come out forthwith. . . .

In Book II, Chapter 16, entitled "Wounds of the Chest, whether Anterior or Posterior," Theodoric continues:

> . . . on whatever side the wound occurs, let the lips be joined together completely and be replaced as nearly as possible in their natural position and let the wound be sewed together accurately; and the stitches should be placed in accordance with the size of the wound, so that the natural heat cannot escape in any way, nor the air outside be able to enter. . . . Put on dressings of good tow, soaked . . . in hot wine and after overlaying these with much dry tow, well suited to keeping in the warmth, bind it up with wide bandages. And leave this dressing alone for five to seven days, if no pain occurs.

Chapter 33 in Book II is an excellent and accurate discourse on fractures of ribs. It lists the cardinal physical signs, and divides these fractures into two types, those which bend in and those angled outward. The latter are considered easier to cure. Theodoric describes the ceaseless pain, the labored breathing, the coughing and bloody sputum that ensue when a rib fragment punctures the visceral pleura. He also cautions that—

> When the bone has punctured the diaphragm, then it is necessary to cut at the point of injury and disclose the broken rib. Protect the pleura by placing an instrument under the rib.

In the next or *fourteenth* century, the Salernitan school of medicine was already in decline, Bologna was known chiefly for Mundinus in anatomy, and the French schools were in their ascendancy, especially Montpellier. The rise of the latter university was related to several factors. First was its geographical proximity to Moorish Spain and thus to the Arabic renaissance; second, a steady influx of persecuted Jewish intellectuals, many of whom had been educated at Cordova; and third, the location of the exiled papacy at Avignon between A.D. 1309 and 1377. The latter circumstance naturally resulted in a steady stream of statesmen, travellers, and students carrying with them new ideas and writings from all Europe and the Byzantine empire.

The leading physician-surgeon of medieval France, and the most illustrious ever to graduate from Montpellier, was Guy (Guido) de Chauliac. Born about 1300, he was, despite his patrician name, the son of a modest farmer in the province of Auvergne. After early tutoring by his parish priest, he matriculated at Toulouse and eventually went to Montpellier where he received the master's degree in medicine in the year 1325. Although he worked for a time in anatomy with Bertuccio, Mundinus' successor at Bologna, his training in surgery must have been of a practical sort because this was not a discipline recognized by the medical faculties of the time. Settling into private practice, he soon earned an outstanding reputation, enjoyed the patronage of the church and its hierarchy, and was appointed physician to Pope Clement VI, and several later Avignon popes, Innocent VI and Urban V. He worked through, and fortunately survived, the Great Plague of 1348.

Guy de Chauliac's writings were not numerous, but his major work *Chirurgia Magna,* when finished in 1365, became immediately and continued to be the standard surgical reference during the remainder of the fourteenth and the fifteenth centuries. It was translated into his native French tongue, also into Spanish, Provençal, English, and Dutch. The definitive translation is the modern French of E. Nicaise, published in 1890.[4]

In Chapter 5 of his second Doctrine, Guy expresses curiosity that Galen, Halyabbas, and Avicenna (among other ancients) had so little to say about thoracic wounds, and points out that more recent authors were in substantial disagreement concerning therapy. One group, which included Roger (Frugardi) of Salerno, Roland of Parma, William of Salicet in Bologna, and Lanfranc of Paris, advocated exclusively the open treatment of penetrating thoracic wounds,

employing tents and drains, so that blood and its putrefactive by-products could escape and healing could ensue secondarily. A smaller group, led by Theodoric and Henri de Mondeville, believed just as firmly that wounds should be closed immediately by suture, if necessary, to minimize the loss of natural heat and the ingress of cold air, a philosophy reminiscent of Theodoric. Guy offers a classification of wound types:

> Wounds of the thorax, whether anterior or elsewhere, may be superficial and non-penetrating or penetrating into the interior. Those which penetrate are sometimes simple with no injury to the contained structures, or complicated with wounds of such organs as the heart, lungs and diaphragm. In either type there may be little or no blood loss into the [pleural] space, or sometimes a great deal. These are the distinctions upon which therapy must be based. . .
>
> The sign of a penetrating wound is the passage of air through the wound even when the patient's mouth and nostrils are closed, as can be demonstrated by a lighted candle, wool or cotton lint applied near the site; testing with a probe or sound is not as conclusive. . .
>
> The signs of a wound in the lung are the issue of bright red and frothy blood, a restless patient coughing and pale, with the wound located around the ribs. . .
>
> One judges that those wounds which penetrate posteriorly are more dangerous than those [placed] anteriorly because of the veins, arteries, esophagus, trachea and cardiac ligaments which lie there.

In treatment, Guy recommends the use of appropriately large bandages for nonpenetrating wounds and for those penetrating without evidence of visceral injury or retained blood. When a penetrating wound is associated with a large accumulation of blood and "materials," he urges no delay in effecting their discharge by dilating the wound margins and inserting a tent, the base of which must be wider than the apex to prevent its falling into the pleural space; a string may be attached. He follows the suggestion of Iamier that the wound be irrigated daily for 4 or 5 days with a measured quantity of warm wine or with *melicratum* (a mixture of honey and river water). The patient is rotated after instillation of the fluid, which is then recovered, measured again, and observed carefully. When the fluid decreases and becomes clear, one discontinues the irrigations and "consolidates" the wound. One always keeps a dressing of old, well-washed cotton in the orifice of the wound to absorb discharges and maintains the patient upon his wounded side to promote drainage. The patient is dressed in this fashion until he is cured, decreasing the size of the tent and the cotton dressing progressively.

When, despite these measures, the clinical course and physical signs indicate retention of materials "upon the diaphragm," Guy follows the recommendation of William of Saliceť, performing an incision placed inferiorly and obliquely along the course of the ribs toward the spine, providing the patient is strong enough to withstand it and willing to accept it (without anesthesia). Guy points out the possibility that the diaphragm may interfere with drainage, and by sealing the incision give the impression that the incision has not been carried deeply enough. Further treatment follows the lines described previously, with tenting and irrigation. As though to bolster his precariously radical

position in this matter, Guy calls upon the ancient authorities and cites the experience of Galen, Halyabbas, and Avicenna in the management of empyema by cautery drainage.

Among the well-known surgeons of the *fifteenth* century was the Italian-born Giovanni da Vigo, surgeon to Pope Julius II. Vigo's chief opus, *Practica Copiosa in Arte Chirurgia,* survived at least 40 editions and translations into five languages, including the English of Thomas Gale in 1586.[5] Vigo described indications for employing suture-ligatures on certain accessible vessels, but he still believed in the venomosity of gunshot wounds, insisting that they be cauterized with hot irons or boiling oil. In Gale's 1586 edition, only nine pages are devoted to "Wounds of the Breast, Called Thorax, and Cure of the Same." This quaint medieval English translation demonstrates a strong resemblance to the words of Guy de Chauliac:

> It chaunceth often that the breast is hurt by pointed thinges, as daggers, dartes, etc. And of them some perce unto the inner partes. Some be onely superficiall, and not percing. Some are with hurt of the contained members, and some without hurt of the same. Moreover, of these woundes persing and not persing, some are in the former part, and some in the hinder. They that are in the hinder part, be more dangerous then the other, for many causes. . .
>
> You may moreover know whether the wound perseth, by the application of cotton well tosed upon the orifice of the wound, and by the holding of a little candle burning nigh to the wound, for the flame thereof shall be moved, and lykewise the cotton, [even] if the patient hold his breath, stopping his mouth and nosethrills.
>
> . . . Before we speake of the curation, we wyll declare the discord that is betweene the Doctors of this time concerning the same. There bee manie that commaund to shut incontinentlie the penetraunt wounde, . . . saying, That if the sayde wound bee not shut, the aire will enter in unto the heart, and moreover, that the vital spirits wil issue out by the wound, which thing might hurt the patient.
>
> Againe, many be of a contrarie opinion, and commaund to keepe the wound open. And if the wound be not large, they saie it must be enlarged that the bloud may issue out, affirming that if the bloud which is in the inner part issue [not] out by the orifice of the wound, it may ingender many evil accidents and corrupt the inner members. . .

Vigo subsequently inclines to support the school which employs the open treatment, although admitting the possibility of wound closure as early as the first day, if there is no problem of retained blood. The last paragraph in this chapter concludes

> . . . And brieflie to finish this Chapter we will give two doctrines profitable in this case. The first, that when the Chyrurgion is called, he must dress it [the wound] as quicklie as maye bee. . . . The second is, the Chyrurgion must prognosticate according to the signes that he shall see, that he may save his name. Nevertheless, the Chyrurgion shal not refuse to cure any hurt of the members contained in the inner part, except ye heart. For Nature by the Chyrurgion's side worketh so well, that oftentimes it bringeth that to passe, that seemeth impossible.

[This note of optimism concerning thoracic wounds represents one of the first encountered in reading of the ancient authors.]

In the *sixteenth* century, Ambroise Paré was not only the greatest surgeon of the Renaissance, but one of its most prominent personalities. He was born near Laval in Moyene (Maine) province, probably in the year 1510, the child of a humble artisan. His brother and two brothers-in-law were barber-surgeons, and he himself was apprenticed at the Hotel Dieu de Paris for a period of 3 years. A very active and, at times, bitter experience with the French armies in a succession of campaigns against the cities of Italy and against Spain gave him an enormous first-hand experience in the management of trauma and in the diseases of camp life. This experience was assimilated with peasant shrewdness, a keen intelligence, complete honesty, and a fine wit, and his knowledge brought him increasing success and a widely spreading reputation. He became personal physician to de Montjean and de Rohan, and eventually to a succession of four French kings, Henry II, Francis II, Charles IX, and Henry III. Returning from the wars in 1545, he enjoyed the friendship of Jacques Du Bois (better known as Sylvius) who was intrigued by Paré's revolutionary proposal for the treatment of gunshot wounds which dispensed with the use of cautery and boiling oils. Paré became prosector for Sylvius and carried out some anatomical dissections at the University of Paris. His friendships among grateful and influential patients were so strong and his professional reputation so great that he was elected to the university's College of St. Cosmos, despite his educational deficiencies, particularly in the Latin which was required for a formal thesis. He wrote in the French vernacular, with a charming simplicity and clarity tinged with a subtle scorn for his empirical medical confreres. Paradoxically, his works were translated first into Latin and thence into English by Thomas Johnson, as early as 1634.

Paré's introduction to Chapter 32, entitled "Des Playes du Thorax ou Poitrine,"[6] is so reminiscent of de Vigo and again of Guy de Chauliac that several excerpts will be translated and quoted in detail:

> Some wounds of the thorax or chest are anterior, others are posterior; some penetrate deeply, others not; some are associated with injuries to the contained parts, such as the mediastinum, lungs, heart, diaphragm, vena cava, and ascending aorta. . . . Therefore, some are lethal and some are not.
>
> The signs of penetration from without are recognized when air escapes the wound with a whistling sound. And to recognize this easily, one occludes the nose and mouth of the patient . . . air will be seen to exit, as one brings near it a lighted candle; the flame flickers, and is sometimes extinguished. . .

Then follows the first description in the literature, very clearly given, of traumatic diaphragmatic hernia:

> The signs demonstrating wounds of the diaphragm are a sensation of heaviness at the site of injury, delirium, . . . great difficulty to respire, cough and severe pain. Because of the overactive breathing, the stomach and intestines are sometimes drawn into the thoracic cavity as I have seen in two cases.
>
> The first, a bricklayer's apprentice, was wounded in the central portion of the diaphragm and died three days later. Having opened the abdomen [at autopsy] I could find no stomach. This mystified me greatly, thinking it a monstrous thing to be without a stomach. . . . I finally realized that it had ascended

into the chest, although the diaphragmatic wound would admit no more than the thumb. Upon opening the chest, I found the aforesaid stomach, distended with air and a little congested.

In addition, at the siege of La Rochelle, a captain Francois D'Alon . . . received an arquebus wound, entering below the sternum close to the xyphoid, and . . . exiting between the left fifth and sixth true ribs. The external wound healed well, but a constant gastric disability remained with him, a sort of colic because of which he ate only sparingly. Eight months later a violent pain began in the epigastrium, and was assiduously treated by M. de Malmedy, Regent of the Medical Faculty and Royal Lecturer, and M. du Val, also a doctor in the medical faculty, men well grounded in both medicine and surgery. Despite available measures, the patient succumbed. I requested an autopsy to determine the cause of death and of the great pain he suffered during his illness. It was performed by Jacques Guillemeau, royal surgeon and a graduate of Paris, who is well versed in anatomy as well as other aspects of surgery. In the thoracic cavity there was discovered a large section of colon filled with air. This had entered through the diaphragmatic wound, although the defect was scarcely large enough to accommodate the tip of the little finger.

In the medical literature of the *seventeenth* century are encountered several interesting reports of thoracic wounds with prolapsed lung treated by amputation of the exposed portions. Perhaps the most widely known case is that recounted by Nicholas Tulp, or Tulpius,[7] professor of anatomy and surgery at Amsterdam, who was the principal subject in Rembrandt's immortal painting, "The Anatomy Lesson of Dr. Tulp." Tulpius tells of a brawling drunkard who sustained a deep wound just beneath the left nipple but was too intoxicated to heed it immediately. The next morning the patient recognized that a portion of lung measuring about three fingers in breadth was extruding from the incision. With the unprotected lung hanging out, the wounded creature undertook a two-day journey on foot to Amsterdam, where Tulpius saw and attended him, cutting off the prolapsing segments. The surgically excised fragment weighed three ounces "Amsterdam measure"; in Tulpius' own words, "Grande mehercules pondus, in viscere tam raro ac levi [an enormous weight for an organ so tenuous and light]." The patient recovered rapidly with only a slight residual cough, but his continuing propensity for revelry led to his eventual demise and involuntary appearance in the anatomical theater 6 years later.

A quite similar case was reported by the German, Fabricius Hildanus, in his *Opera Omnia,*[8] published posthumously in 1646, and was mentioned again by Laurence Heister in a footnote to his *Chirurgie,* dated 1724.[9] Heister clearly realized the necessity for keeping the pleural cavity air-tight by assiduously avoiding any manipulation of the prolapsed pulmonary tissues until they were firmly adherent to the wound margins. This was, of course, a sound principle of pulmonary surgery during its formative stages and even until the early years of the present century—witness the two-stage techniques for lobectomy and cautery pneumonectomy which were practiced in the 1920's and 1930's.

Illuminating the state of affairs at the beginning of the *eighteenth* century are the writings of Hermann Boerhaave, in his time a world-renowned professor of chemistry, botany, and medicine at the University of Leyden. The son of a country parson and completely trained for the ministry before he pursued his

medical studies, Boerhaave was a person of fabulously encyclopedic knowledge but not usually remembered for his surgical writings. Nevertheless, he gave medicine its first complete clinicopathologic description of spontaneously ruptured esophagus, in the famous case of Baron de Wassenaer, grand admiral of the Dutch Navy; also, one of the first recognizable records of a mediastinal tumor, perhaps a lipoma. Boerhaave's *Aphorisms*,[10] collected by his pupil Gerard van Swieten, founder of modern Viennese medicine, and published posthumously in Latin, include a section entitled "Wounds of the Thorax," comprising Aphorisms 297 to 305. Each is a relatively short paragraph, and as a group they are eminently sensible and sometimes quite modern in tenor. However, with limitations as to space, only one must suffice here:

> 303. It is necessary to evacuate the extravasated blood [from the pleural cavity in traumatic hemothorax] by 1) posturing the patient and by appropriate exercises; 2) suction applied through a blunt-tipped flexible tube perforated laterally; 3) the injection of anticoagulant fluids; 4) enlarging the wound; 5) making a counterincision between the two lowest true ribs, four fingerbreadths from the vertebrae and the inferior scapular angle, using a bistoury directed inferiorly, the incision placed between and parallel to the two ribs.

Thus were anticipated in the early 1700's the concepts of postural drainage, intercostal suction catheter drainage, and chemical alteration of the exudate to promote its evacuation. However, the concept of thoracotomy may well have been encountered by Boerhaave in his reading of William of Salicet, Guy de Chauliac, or the much earlier Galen and Celsus.

The state of affairs at the close of the *nineteenth* century is documented in the writing of Stephen Paget,[11] London surgeon, and author in 1896 of the first English text devoted entirely to thoracic surgery. In a chapter entitled "Wounds of the Lung," Paget emphasizes that most wounds of the chest have a medico-legal aspect and careful note must be made of

> . . . the whole scene, the position and condition of the patient, the shape, size and staining of the weapon, and the exact character and measurement of the wound. . . . External hemorrhage, if present, must be checked at least temporarily by firm pressure; and the worst of the shock must be overcome by warmth to the extremities, hypodermics of strychnine and careful stimulation. . .
>
> We have to consider here those wounds that afford clear evidence of lung injury; and this evidence is hemorrhage, external through the wound, effused into the pleural cavity, running into the bronchi, escaping into the mouth; the signs of loss of blood—pallor, bloodless tint of the lips, faintness, quick feeble pulse, hurried sighing respiration, cold hands and feet, and marked restless oppression and sense of impending dissolution; and the physical signs of effusion.

Paget goes on further to discuss hemoptysis, hemorrhage into the pleura, and hemorrhage from the wound. His descriptions exemplify the progress made in physical diagnosis by Auenbrugger's introduction of the percussion method in 1761,[12] and Laennec's stethoscopic auscultation in 1819.[13] Paget continues

> It is the same internal hemorrhage in gunshot wounds, that accounts for a great number of deaths on the field of battle. . . . The mortality from such wounds in time of war is probably not less than 60 percent of all chest wounds

> classed as penetrating, and much higher than this for actual gunshot wounds into the lung. After Sedan [1870], Sir William McCormac reported that of 54 cases treated in the Anglo-American Ambulance at Asfel, 31 were regarded as penetrating, of which 17 died. From Metz, Dr. Fischer reported 78 cases, of which 34 were perforating gunshot wounds; of these 34, 19 died. . .
>
> As regards the use of the probe there is some difference of opinion. . . . In an incised or punctured wound, it is better not to use it. It is in gunshot wounds that the probe may be needed, but perhaps not at first. And even here, as we see from the case reported by M. Pean, its use may lead to bad results. . .
>
> There is a wide difference between rash and unwarrantable explorations and the judicious use of the probe and forceps in cases in which there are just grounds for suspecting the presence of a foreign body. . . . It is almost needless to repeat that all good surgeons agree that the finger is the best probe whenever available.
>
> Of all penetrating wounds of the chest, it may be said that they must only be closed, providing the surgeon be at hand to reopen them, if necessary. Mere compression of the lung by the blood effused will tend to arrest bleeding. Puncture and aspiration may be necessary. But if the bleeding still goes on, then the surgeon's last resource must be an operation, freely exposing the lung, and enabling him to plug or suture the wound in it, or apply a ligature at the source of hemorrhage. As regards this operation . . . the three following cases (1885, 1893, and 1894) illustrate with what degree of success this dangerous measure may be carried out.

Paget then presents a synopsis of Omboni's case at Cremona, a youth of 20 who shot himself in the left chest with a revolver. After signs of grave collapse developed, the left chest was opened through a 5-inch incision, a large quantity of blood evacuated, the wounded anterior portion of the upper lobe ligated with catgut, and excised. At first the patient did well, but suppuration intervened to cause his death. The second case (Delorme's) was an army officer, who stabbed himself in the left chest with an amputating knife. Two days later, because of persistent bleeding, the chest was freely opened. Three wounds in the lung and two of the pericardium were sutured. The patient succumbed a quarter of an hour postoperatively.

The third and only successful case was that reported by Michaux; the patient was a youth of 18 who shot himself just outside of the left nipple. Because the signs suggested internal bleeding, operation was performed the following day. The bleeding point was discovered on the inner aspect of the lung, just below the hilum. The bleeding point was plugged with a strip of iodoform gauze, bringing the end outside of the chest, and draining the pleural cavity with two large tubes. Despite slight suppuration, the patient made a splendid recovery. Paget concluded

> Thus, the matter stands; at any rate, we must be prepared, should all other measures fail, to attempt to find and secure the wound in the lung, for we must remember Ch. Nelaton's statistics (Thesis, University of Paris, 1880). Of 86 cases of penetrating wound of the chest with hemorrhage into the pleura, only 22 recovered without operation; 20 were treated by puncture or incision of the chest, to relieve the pressure of the effused blood, and 4 of them died; 44 died of hemorrhage without operation.
>
> As to the removal of foreign bodies after the patient has recovered from his wound, each case must be decided on its own merits. So far as I know, the

Röntgen rays have not yet been employed for this purpose; and von Bergmann has recently warned us that, even if a foreign body can be exactly localized by means of them, it may still be wrong to interfere with it.

Although the year 1842 had witnessed the employment of ether anesthesia by Crawford Long of Georgia, and in 1844 the ill-fated Hartford dentist, Horace Wells, anesthetized himself with nitrous oxide for a tooth extraction, it was not until the opening years of the present century that the special problems posed by surgery within the open chest were solved. The late Ferdinand Sauerbruch's abortive experiments with the cumbersome "Unterdruckskammer" came to an end about the time (1909) that Meltzer and Auer of New York described endotracheal positive pressure insufflation. While Meltzer's paper[14] gave the necessary impetus to many subsequent technical refinements, the concept of endotracheal intubation actually dates back to experiments performed upon animals by Robert Hooke in 1667,[15] and even earlier by Vesalius in the middle of the sixteenth century.[16]

After these important developments in anesthesia, and the advent of methods for typing of blood and its preservation, and following the discovery of the chemotherapeutic sulfonamides, the stage was set for certain therapeutic advances which occurred in World War II. One was the revival and perfection of the decortication procedure for organizing hemothorax and empyema, first performed by Fowler in 1893[17] and Delorme in 1894.[18] Great progress was also made in the surgical management of wounds involving the heart and great vessels, the prototype of which was Rehn's successful cardiorrhaphy in 1897.[19]

Without elaborating upon these more modern contributions, it will suffice to report that the over-all mortality among U. S. soldiers treated for thoracic wounds during World War II was reduced to 9 per cent as compared with approximately 24 per cent in World War I. In the recent Korean war, the thoracic wound mortality was held to the amazingly low level of 5 per cent.[20]

Members of the surgical profession may take justifiable pride in these accomplishments and credit for having trained the remarkable group of young soldier-surgeons who applied their newly gained knowledge with such splendid effect. These youthful military surgeons, heirs to the tradition of Ambroise Paré, will understand why it is appropriate to close an incomplete review of seven centuries of experiences with thoracic trauma by recalling the admonishment of that fifteenth century surgeon, Giovanni da Vigo, as he wrote in his *Chirurgia*[5]:

"For Nature by the Chyrurgeon's side worketh so well, that often times it bringeth that to pass, that seemeth impossible."

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THE EFFICIENCY OF VENTILATION WITH VARIOUS METHODS OF CONTROLLED VENTILATION

A Study of Total Ventilation, Alveolar Ventilation, and Efficiency of Ventilation in Anesthetized Dogs

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RESPIRATORY ACIDOSIS may occur frequently during inhalation anesthesia for surgical operations.[2, 7-11, 15, 16, 20] This is avoided by increasing the total volume of ventilation sufficiently to dissipate the carbon dioxide which tends to accumulate.[1, 17] When ventilation is mechanically or manually controlled with the thorax open, previous studies have indicated that the total ventilatory volume must be increased disproportionately in order to maintain an adequate alveolar ventilation,[1, 9, 17, 20] a decrease in the efficiency of ventilation. This has been attributed to (1) incomplete carbon dioxide absorption, (2) poor ventilation-perfusion ratios, and (3) an increased respiratory rate with a disproportionate amount of the total ventilatory volume moving to and fro through the dead space of the respiratory tract.[16, 20] It was thought the second factor was possibly primarily related to alveolar capillary occlusion secondary to increasing the pressure within the bronchial tree with a consequent loss of ventilatory efficiency. When the work required to provide an adequate volume of ventilation is considered, the efficiency of ventilation is of practical significance.

This study was designed to compare the efficiency of ventilation in the dog using these methods: (1) spontaneous respiration; (2) positive intratracheal pressure inflation, ambient pressure deflation of the lung; (3) positive intratracheal pressure inflation, vacuum deflation of the lung; and (4) ambient intratracheal pressure, with thoracic cage exposed to varying pressure in a tank respirator. Alveolar ventilation, total ventilation, and efficiency of ventilation were determined. Comparable pressure differentials were used in the last two methods. Both inflation and inflation-deflation pressures were used.

METHODS

Twenty-two mongrel dogs, weighing between 9.5 and 18.3 kilograms (the majority weighing 13 to 15 kilograms), were premedicated with 15 mg.

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morphine sulfate and 0.4 mg. atropine sulfate. Thirty minutes later they were anesthetized with pentobarbital administered intravenously in a dosage of 30 mg. per kilogram. Thirty to 60 minutes after anesthesia the ventilatory measurements were begun. The dog was breathing regularly and spontaneously 8 to 12 times per minute. When using mechanically controlled ventilation, the respiratory rate was 16 per minute and the ratio of duration of inspiratory phase to expiratory phase was 1:1. A pressure differential of 15 mm. Hg was used between the inspiratory and expiratory phases of ventilation.

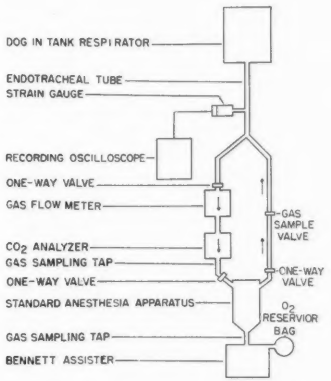

Fig. 1.—Diagram of anesthesia closed circuit and interposed measuring devices.

A diagram of the apparatus is shown in Fig. 1. The Bennett Assister Model SD 2, driven by oxygen, is a pressure-cycled ventilator which delivers oxygen to a Foregger closed circuit anesthesia apparatus from a 2-liter reservoir. A 5-liter rebreathing bag is connected to a separate 3-way orifice on the side of the Bennett Assister. This bag can be used to fill the reservoir of the Bennett Assister during experiments. It is also used as a source of oxygen when the dog is breathing spontaneously or when using the tank respirator. The dog can be ventilated with oxygen for periods of more than 5 minutes without requiring addition of oxygen and without extraneous changes of the initial volume or composition of gas in the system.

The oxygen delivered to the Foregger closed circuit machine flows through new standard corrugated rubber anesthesia tubing to an endotracheal tube. The volume of expired gas is next measured by a dry gas flowmeter having a flow capacity of 5 to 150 cubic feet per hour with resistance of less than 0.5 cm. of water at higher flows. This flowmeter has a dead space of 16 liters. The meter was found to be an adequate mixing chamber for the expired gas which was monitored continuously by a Beckman carbon dioxide infrared analyzer connected distal to the flowmeter. Three-way stopcocks were placed distal to the anesthesia machine on the inspiratory line and distal to the carbon dioxide analyzer on the expiratory line for sampling inspiratory and expiratory gases for carbon dioxide on test. The carbon dioxide concentration was measured

by a Beckman gas chromatograph which was calibrated at intervals with known gas samples determined by the micro-Scholander technique.[19] Fresh soda lime was added before each experiment.

During spontaneous breathing or during controlled ventilation using the Bennett · Assister, the endotracheal pressure was measured with a Statham pressure transducer (Model No. P23A) attached to the proximal end of the endotracheal tube. When the dog was in the tank respirator, the intra-tank pressure was measured by attaching the pressure transducer to an outlet on the tank. The pressures were precisely adjusted and displayed and recorded from a cathode ray tube. Sample records are shown in Fig. 2.

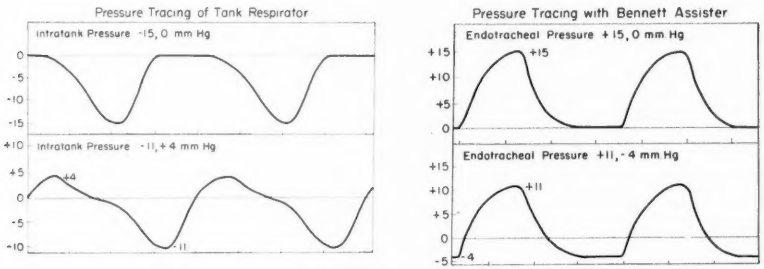

Fig. 2.

All gas volumes were corrected to standard conditions (STPD).

A Cournand needle was placed in the femoral or carotid artery and blood samples were drawn in oiled syringes containing a drop of mercury and a small quantity of heparin. These arterial samples were drawn at the end of the experiment simultaneously with the gas samples. The pH was determined promptly using a Cambridge glass electrode pH meter calibrated with standard buffer solution before each determination. Oxygen and carbon dioxide content were determined by the manometric method of Van Slyke and Neill.[21] Oxygen capacity was calculated by multiplying the hemoglobin content of the blood, determined with a Coleman spectrophotometer, by 1.34, the accepted figure of oxygen capacity per gram of hemoglobin. The plasma carbon dioxide content was determined using the nomogram of Van Slyke and Sendroy.[22] Using this value and the pH, the pCO_2 of arterial blood was then read from the nomogram. When the pCO_2 could not be read from the nomogram, it was calculated by the Henderson-Hasselbalch equation using the formula[6]:

$$pCO_2 = \frac{\text{Total } CO_2 \text{ of plasma in millimoles/liter}}{0.0301\ [\ (10pH - pK) + 1\ ]}$$

Alveolar ventilation was calculated from the formula[5, 16]:

$$V_A = \frac{Fe\ CO_2 - Fi\ CO_2}{Fa\ CO_2 - Fi\ CO_2} \times V_E$$

$Fe\ CO_2$ = per cent of CO_2 in mixed expired gas.
$Fi\ CO_2$ = per cent of CO_2 in inspired gas.
$Fa\ CO_2$ = per cent of CO_2 in the alveoli.
V_E = volume of expired gas (L./min.).

Since the CO_2 in arterial blood is assumed to be equal to that in the alveoli, the pCO_2 of blood can be used to calculate Fa CO_2 as follows:

$$\text{Fa } CO_2 = \frac{pCO_2}{P_B - 47}$$

P_B = prevailing barometric pressure.
47 = water vapor pressure at body temperature.

The efficiency of ventilation was determined by dividing the alveolar ventilation by the total ventilation.

An important consideration in the measurement of gas flow in the system used in these experiments is the effect of alternate compression and decompression of the gas when intermittent positive or intermittent positive-negative endotracheal pressure is used. Boyles' law states that at a constant temperature the volume of any gas varies inversely as the pressure to which the gas is subjected ($P_1 V_1 = P_2 V_2$). In the system in Fig. 1, the flowmeter had a volume of 16,700 ml., five corrugated rubber tubes had a volume of 550 ml. each, a short plastic tube on the Bennett Assister had a volume of 135 ml., three one-way valves had a volume of 37 ml. each, a soda lime cannister had a volume of 628 ml., and three rubber connectors had a volume of 50 ml. each. The total volume was 20.48 liters (ambient). With 15 mm. Hg increase in pressure, the volume would change to 20.07 L., a decrease of 0.41 L. per respiration. At a respiratory rate of 16 per minute, there would be a theoretical flow of 6.56 L./min. (ambient) or 5.97 L./min. (STPD) due to the one-way valves in the closed system. In the usual anesthetic system without the additional measuring and monitoring apparatus, the volume decreases from 2.49 L. (ambient) to 2.44 L. (ambient) with an increase of 15 mm. Hg pressure. This would produce a theoretical flow of 0.8 L./min. (ambient) or 0.73 L./min. (STPD) at a respiratory rate of 16 per minute. When the flow around the circuit was actually measured by clamping the endotracheal tube and recording the volume on the flowmeter at pressures + 15, 0 and + 11, – 4, an average of 6.69 L./min. (STPD) was found (Table I). The difference between 6.69 L. and 5.97 L. is due in part to the distensibility of the corrugated tubing in the system.

TABLE I. GAS FLOW AROUND A CLOSED ANESTHESIA CIRCUIT WITH THE ENDOTRACHEAL TUBE OCCLUDED USING THE BENNETT ASSISTER

	FLOW IN LITERS PER MINUTE AT RATE OF 16 PER MINUTE
Pressure + 15, 0 mm. Hg	
	7.42
	7.13
	7.25
	7.14
Pressure + 11, – 4 mm. Hg	
	7.80
	7.42
	7.61
	7.55
Average	7.42
Average (STPD)	6.69 L./min.

These data show that there is considerable flow around the circuit in the experimental apparatus which does not go to the lungs but is recorded on the flowmeter each time there is a fluctuation of pressure. Therefore, in order to calculate the correct volume flow to the lungs during intermittent positive or intermittent positive-negative endotracheal ventilation, 6.69 L./min. was subtracted from the recorded volume on the flowmeter (Table I).

The per cent alveolar ventilation using the Bennett Assister is calculated as follows:

$$\text{per cent } V_A = \frac{V_A \text{ (STPD)}}{V_E \text{ (STPD)} - 6.69 \text{ L./min.}}$$

V_A = volume alveolar gas (L./min.)
V_E = volume expired gas (L./min.)

EXPERIMENTAL PROCEDURE

Total ventilation was measured and the alveolar ventilation and per cent alveolar ventilation were calculated in anesthetized dogs with the thorax open and with the thorax closed under the following conditions: (1) dog breathing spontaneously (with the thorax closed); (2) during ventilation with intermittent positive pressure of + 15, 0 mm. Hg using the Bennett Assister; (3) during ventilation with alternating positive-negative pressure of + 11, – 4 mm. Hg using the Bennett Assister; (4) during ventilation with intermittent negative intra-tank pressure of – 15, 0 mm. Hg using the Columbian tank respirator; and (5) during ventilation with intermittent negative-positive pressure of – 11, + 4 mm. Hg using the Columbian tank respirator.

The anesthetized and intubated dog was placed in the right semilateral position and a systemic artery was exposed. Ventilatory measurements were done with the closed system as shown in Fig. 1. The re-breathing bag was filled with oxygen (but not overdistended) and the volume of expired gas was read from the flowmeter while the dog was breathing spontaneously. Gas samples and the arterial blood sample were then drawn. The endotracheal and the intra-tank pressures were recorded. The studies using the Bennett Assister and the tank respirator were done in varying sequences. The thorax was opened using an incision through the fifth intercostal space. Studies using the Bennett Assister and the tank respirator were repeated.

An error in method was found in the early tank respirator studies in taking the blood samples. Initially, the samples were obtained by opening a side panel on the tank. No ventilation pressures existed during the 5 to 15 seconds required for sampling. A rapid decrease in pH and per cent alveolar ventilation and an increase in pCO_2 occurred. Subsequently, samples were taken through a plastic tube which was connected to a three-way stopcock on the outside of the tank. In order to do this it was necessary to heparinize the dog. The static blood in the tube was first aspirated and then reinjected after the blood sample was taken.

RESULTS

1. *Dog Breathing Spontaneously* (Table II).—The total ventilation and alveolar ventilation were less than in any of the methods of assisted ventilation

TABLE II. VENTILATION IN ANESTHETIZED DOGS BREATHING SPONTANEOUSLY

DOG NO.	WEIGHT (KG.)	TOTAL VENTILATION (L./MIN.)	ALVEOLAR VENTILATION (L./MIN.)	ALVEOLAR VENTILATION (PER CENT)	pCO_2 (MM. HG)	pH	O_2 SATURATION (PER CENT)
3	14.7	2.25	.645	28.61	70	7.20	102
2	13.9	1.972	.254	12.85	94.4	7.10	102.3
49	18.3	1.361	.500	36.7	69.0	7.15	80.4
3	15.0	1.485	.539	36.25	72.0	7.22	95.48
5	16.4	1.295	.313	24.19	66.0	7.11	95.5
49	18.3	1.05	.252	24.6	86.0	7.03	9.5
315	15.0	1.165	.335	28.79	88.0	7.06	102.0
5	16.0	.68	.261	38.4	82.5	7.09	98.8
49	17.9	1.611	.473	29.3	53.0	7.22	97.0
3	14.3	1.396	.385	27.6	74.0	7.20	101.4
2	1.34	1.439	.359	25.0	76.0	7.17	106.0
61	13.4	1.27	.522	41.1	57.0	7.26	102.0
62	1.37	3.36	1.082	32.25	48.5	7.21	97.5
63	12.4	2.42	.840	34.7	51.8	7.26	98.5
Average		1.622	.483	30.05	70.5	7.17	98.4
Range		.68-3.36	.252-1.082	12.85-41.1	48.5-94.4	7.03-7.26	95.48-106.0

TABLE IIIA. CONTROLLED VENTILATION IN ANESTHETIZED DOGS USING THE BENNETT ASSISTER

DOG NO.	WEIGHT (KG.)	TOTAL VENTILATION (L./MIN.)	ALVEOLAR VENTILATION (L./MIN.)	ALVEOLAR VENTILATION (PER CENT)	pCO_2 (MM. HG)	pH	O_2 SATURATION (PER CENT)
Endotracheal Pressure + 11, − 4 mm. Hg (Thorax Open)							
5	16.0	4.61	1.073	23.3	53	7.26	96.7
49	17.9	5.46	1.93	35.35	33	7.36	98.9
3	14.3	3.01	1.205	40.1	44	7.35	87.0
2	13.4	3.52	1.021	29.1	37	7.44	97.7
61	13.4	10.85	3.90	35.9	12	7.72	103.0
62	13.7	6.81	3.44	50.5	21	7.43	97.1
63	12.4	6.21	3.41	54.9	21	7.50	93.4
66	11.7	3.44	1.32	38.4	27	7.41	94.0
67	11.0	4.73	1.37	29.0	28.8	7.37	94.0
68	9.63	4.61	1.63	35.3	18.8	7.51	104.5
69	9.5	4.87	1.17	24.0	23.8	7.39	99.3
70	10.6	10.11	2.62	25.85	16	7.58	100.0
71	11.7	3.96	1.25	31.6	32.9	7.31	89.2
Average		5.55	1.95	34.8	28.2	7.44	96.7
Range		3.01-10.85	1.021-3.90	23.3-54.9	12.0-53.0	7.26-7.72	87.0-104.5
Endotracheal Pressure + 15, 0 mm. Hg (Thorax Open)							
5	16.0	6.03	2.205	36.6	32	7.46	103.0
49	17.9	7.72	4.03	52.3	21.0	7.53	103.7
3	14.3	6.03	2.16	35.9	32.9	7.44	100.0
2	13.4	4.51	1.449	32.08	31	7.49	100.5
61	13.4	13.01	6.53	50.01	6.63	7.86	103.0
62	13.7	9.03	5.55	61.5	14.0	7.57	100.2
63	12.4	7.96	5.40	67.9	13.0	7.61	98.1
66	11.7	5.71	3.35	58.6	18.8	7.54	99.0
67	11.0	7.11	4.03	56.6	13.0	7.62	102.0
68	9.63	8.41	4.87	58.0	6.87	7.68	107.0
69	9.50	6.61	2.58	39.09	15.8	7.56	102.5
70	10.6	12.43	6.65	53.5	6.94	7.73	105.0
71	11.7	8.01	2.49	31.1	18.2	7.42	100.5
Average		7.90	3.94	48.6	17.7	7.58	102.0
Range		4.51-13.01	1.449-6.65	31.1-67.90	6.63-32.9	7.42-7.86	98.1-107.0

studied. The per cent of alveolar ventilation was less than in any method of assisted ventilation with the thorax closed. This is the only situation in which respiratory acidosis developed with the thorax closed. The arterial pCO_2 average was 70.5 mm. Hg, the pH average was 7.17, and the oxygen saturation average was 98.4 per cent.

2. *Comparison of Inflation and Inflation-Deflation Pressures During Mechanically Controlled Ventilation.*—The total ventilation and the alveolar ventilation were always greater at + 15, 0 mm. Hg than at + 11, – 4 mm. Hg when using the Bennett Assister if the thorax was open (Table IIIA). This was also true when using the tank respirator at pressures of – 15 mm. of mercury when the thorax was either open or closed (Table IV). When the thorax was closed the total ventilation was usually greater with pressures of + 15, 0, but the alveolar ventilation showed no consistent difference, usually a slightly greater volume of alveolar ventilation was recorded at pressures of + 11, – 4 mm. Hg (Table IIIB).

TABLE IIIB. CONTROLLED VENTILATION IN ANESTHETIZED DOGS USING THE BENNETT ASSISTER

DOG NO.	WEIGHT (KG.)	TOTAL VENTILATION (L./MIN.)	ALVEOLAR VENTILATION (L./MIN.)	ALVEOLAR VENTILATION (PER CENT)	pCO_2 (MM. HG)	pH	O_2 SATURATION (PER CENT)
Endotracheal Pressure + 15, 0 mm. Hg (Thorax Closed)							
3	14.7	6.73	2.49	37.0	24.2	7.51	102.0
2	13.9	7.91	2.29	28.95	31	7.47	98.8
49	18.3	7.61	3.25	42.7	26.5	7.44	78.5
3	15.0	6.43	3.20	49.8	30.0	7.52	100.0
5	16.4	8.84	1.851	20.98	52.0	7.20	93.4
5	16.7	8.46	2.85	33.68	27.0	7.43	100.9
49	18.3	7.5	2.18	29.0	50.0	7.23	99.3
3	15.0	7.01	2.79	39.8	28.0	7.48	101.1
Average		7.58	2.62	35.2	33.6	7.42	96.8
Range		6.43-8.84	1.851-3.25	20.98-49.8	24.2-52.0	7.20-7.54	78.5-102.0
Endotracheal Pressure + 11, – 4 mm. Hg (Thorax Closed)							
3	14.7	6.61	2.67	40.4	25.6	7.51	99.7
2	13.9	7.18	2.58	35.98	31.0	7.48	98.9
49	18.3	6.61	3.36	50.9	22.0	7.51	90.0
3	15.0	6.66	2.39	35.9	36.0	7.44	98.7
5	16.4	7.70	2.05	26.65	31.0	7.40	97.9
5	16.7	7.56	1.362	18.05	57.0	7.24	75.0
49	18.3	5.70	2.75	47.7	27.0	7.47	103.7
3	15.0	6.29	2.813	44.8	31.0	7.45	100.2
Average		6.80	2.50	37.6	32.6	7.44	95.5
Range		5.70-7.70	1.362-3.36	18.05-50.9	22.0-57.0	7.24-7.51	75.0-103.7

The per cent alveolar ventilation showed similar changes, although findings were not as consistent. The per cent of alveolar ventilation was rather consistently higher and the average slightly higher (38 per cent compared to 35 per cent) using a vacuum deflation phase with the Bennett Assister when the thorax was closed.

3. *Comparison of Bennett Assister and Tank Respirator.*—With the thorax closed or with the thorax open the total ventilation was greater with the Bennett Assister than with the tank respirator at comparable pressures. The

alveolar ventilation was also always greater with the Bennett Assister except when comparing + 15, 0 mm. Hg with – 15, 0 mm. Hg with the thorax closed. The averages, under these circumstances, were nearly equal (2.62 L./min. and 2.63 L./min.). There was no significant difference in the per cent alveolar ventilation between the Bennett Assister and the tank respirator at comparable pressures except possibly when using + 15, 0 mm. Hg and – 15, 0 mm. Hg with the thorax closed ($p < 0.05$ and > 0.025 using the t test).

TABLE IV. CONTROLLED VENTILATION IN ANESTHETIZED DOGS USING THE TANK RESPIRATOR

DOG NO.	WEIGHT (KG.)	TOTAL VENTILATION (L./MIN.)	ALVEOLAR VENTILATION (L./MIN.)	ALVEOLAR VENTILATION (PER CENT)	pCO_2 (MM. HG)	pH	O_2 SATURATION (PER CENT)
Intra-Tank Pressure – 15, 0 mm. Hg (Thorax Open)							
66	11.7	6.90	1.78	25.81	16	7.53	99.0
67	11.0	5.46	2.73	50.0	13.9	7.50	98.2
68	9.63	6.85	2.87	42.0	10.2	7.55	102.5
69	9.50	5.83	2.63	45.1	11.0	7.33	100.0
70	10.6	9.32	3.56	38.2	10.2	7.55	106.0
71	11.7	5.05	1.92	38.05	24.4	7.31	92.0
Average		6.58	2.58	39.9	14.3	7.48	99.7
Range		5.05-9.32	1.78-3.56	25.81-50.0	10.2-24.4	7.31-7.55	92.0-106.0
Intra-Tank Pressure – 11, + 4 mm. Hg (Thorax Open)							
66	11.7	3.92	1.155	29.5	26.8	7.40	94.0
67	11.0	1.99	.537	27.0	42.0	7.22	74.2
68	9.63	3.53	.960	27.2	20.2	7.35	99.5
69	9.50	3.18	1.075	33.85	21.2	7.24	80.2
70	10.6	6.20	2.06	33.25	15.4	7.51	103.8
71	11.7	2.60	.687	26.4	41.9	7.18	89.4
Average		3.57	1.08	29.6	27.9	7.32	90.4
Range		1.99-6.20	.537-2.06	26.4-33.85	15.4-42.0	7.18-7.51	74.2-103.8
Intra-Tank Pressure – 15, 0 mm. Hg (Thorax Closed)							
66	11.7	6.0	2.67	44.6	21.4	7.54	101.9
67	11.0	5.3	2.22	42.0	23.5	7.47	103.0
68	9.63	5.90	3.21	54.5	18.6	7.64	106.5
69	9.50	4.49	2.31	51.6	25.0	7.52	101.6
70	10.6	5.79	2.66	46.0	23.5	7.52	104.5
71	11.7	5.29	2.68	50.7	20.9	7.48	105.0
Average		5.46	2.63	48.2	22.2	7.53	103.7
Range		4.49-6.0	2.22-3.21	42.0-54.5	18.6-25.0	7.47-7.64	101.6-106.5
Intra-Tank Pressure – 11, + 4 mm. Hg (Thorax Closed)							
66	11.7	5.03	1.67	33.2	23.0	7.51	102.3
67	11.0	4.40	1.89	43.05	18.8	7.58	104.5
68	9.63	4.93	2.09	42.5	17.5	7.64	108.3
69	9.50	4.12	1.57	38.18	32.0	7.54	104.0
70	10.6	5.63	2.26	40.2	22.2	7.54	101.7
71	11.7	4.87	2.47	50.7	21.1	7.48	103.0
Average		4.83	2.00	41.3	21.0	7.55	103.9
Range		4.12-5.63	1.57-2.47	33.2-50.7	17.5-23.0	7.48-7.64	101.7-108.3

4. *Effect of Open Thorax.*—

a. *Using the Bennett Assister at + 15, 0 mm. Hg:* The average total ventilation was slightly greater in the open thorax. The average alveolar ventilation was significantly greater in the open thorax ($p < 0.001$). The

average per cent alveolar ventilation was also significantly greater in the open thorax ($p < 0.02$ and > 0.01).

b. *Using the Bennett Assister at + 11, – 4 mm. Hg:* Total ventilation was decreased in the open thorax when compared to that of the closed thorax. The alveolar ventilation and the per cent alveolar ventilation were also decreased, but the decrease was not significant in either.

c. *Using the tank respirator at – 15, 0 mm. Hg:* Total ventilation was greater when the thorax was open than when closed. The alveolar ventilation and the per cent alveolar ventilation were less in the open thorax but the decrease was not significant in either.

d. *Using the tank respirator at – 11, + 4 mm. Hg:* The average total ventilation was less when the thorax was opened than when closed. The alveolar ventilation was significantly less in the open thorax ($p < 0.02$ and > 0.01). The per cent alveolar ventilation was also significantly less in the open thorax ($p < 0.02$ and > 0.01).

The most efficient system was the Bennett Assister at + 15, 0 mm. Hg with the thorax open. The total and alveolar ventilation were also greatest under these conditions. The arterial blood studies also revealed the greatest respiratory alkalosis under these conditions. The average values were pCO_2, 17.7 mm. Hg; pH, 7.58; and per cent oxygen saturation, 102 per cent.

The least efficient system was the tank respirator at – 11, + 4 mm. Hg with the thorax open. The total and alveolar ventilation were also lowest under these conditions with the exception of the dog's breathing spontaneously. The average pH was 7.32. This was the only condition using controlled ventilation in which the average pH fell below 7.42. The average pCO_2, however, was 27.9 mm. Hg. This was also the only study in which oxygen desaturation occurred (90.4 per cent).

DISCUSSION

Respiratory acidosis occurs in anesthetized patients with unassisted ventilation.[7, 20] This is also shown in our studies in the dog breathing spontaneously after premedication and anesthesia. The acidosis is secondary to hypoventilation, due, in part, to the depression of the respiratory center secondary to anesthetic agents.

Previous reports have indicated that with intermittent positive endotracheal pressure ventilation, the total ventilation increased in the open thorax while the effective (alveolar) ventilation remained essentially the same.[9, 17, 20] In some instances this inefficiency of ventilation is probably related to the method of measurement, the flow of gas around the closed anesthesia circuit with fluctuation of pressure within the one-way closed system. As demonstrated, this flow around the circuit in the normal anesthesia system, unaltered by devices for measurement, is relatively insignificant, measuring only 0.7 L./min. compared to the 6.69 L./min. flow occurring in the system described.

Therefore, we feel that ventilation accomplished by intermittent positive endotracheal pressure (IPP) or positive-negative endotracheal pressure (PNP)

is not inefficient but the apparent inefficiency has been due to an error of measurement. These studies show IPP or PNP ventilation is more efficient than tank ventilation.

Hyperventilation, as shown by the blood studies, was present in all the experiments using controlled ventilation except possibly when using tank ventilation at – 11, + 4 mm. Hg pressure when the thorax was open.

The degree of lung inflation and deflation as observed in the open thorax varied with the different studies even though the pressure differential remained 15 mm. Hg. With the Bennett Assister pressure of + 15, 0 mm. Hg the lung was often tense and overdistended when compared with the lung ventilated with the Bennett Assister at + 11, – 4 mm. Hg pressures. The lung appeared to collapse more during the vacuum deflation phase. With the tank respirator at – 15, 0 mm. Hg the lung appeared similar to + 11, – 4 mm. Hg with the Bennett Assister, although it was usually still more inflated. With the tank respirator at – 11, + 4 mm. Hg, the lung collapsed more and inflated less than at any other pressure. The blood studies show that this was ineffective ventilation.

Gordon, Frye, and Langston[10] have also shown that a greater total ventilation occurs with IPP than PNP with pressures of 15 mm. Hg or less. At end expiration following PNP, the residual volume is less than IPP and in some parts of the lung the alveoli and bronchioles may be collapsed and in apposition. Radford, Lefcoe, and Mead[18] have shown that surface tension tends to hold the walls of alveoli and bronchioles together and make the lung less compliant. The pressure required to inflate the lung is greater in a lung with partially collapsed alveoli than in a lung already partially distended at the resting expiratory level. Therefore, with the same pressure differential, the lung will inflate more with IPP than with PNP. Another factor may be the fact that the compliance of the lung is inversely proportional to the amount of blood in the lung.[11]

In comparing the closed and open thorax, Gordon and associates[10] found similar results in the open thorax except that in the open thorax the differences in the volume of ventilation were never significant. In the open thorax the lung collapses and the end expiratory resting stage is nearly the same with IPP or PNP due to the loss of intrathoracic vacuum. Therefore, with IPP, a slightly greater inflation pressure is required in the open thorax. The increased total ventilation in the open thorax may be explained by the increased compliance.[4]

In studies comparing IPP, PNP, and the tank respirator, others have reported that ventilation by positive pressure endotracheal ventilation is the same as that in the tank respirator.[13, 14] This is theoretically true, but is not substantiated by these measurements in the dog.

In this study no attempt was made to study the effects of IPP and PNP on cardiac output and venous return. It has been shown that in the closed thorax, IPP results in a fall in blood pressure, especially in hypovolemic patients.[13] In the open thorax there is no significant difference between the

effects of IPP and PNP on the cardiovascular system.[10] PNP can, however, be beneficial in aiding deflation in emphysematous patients, and in providing better surgical exposure concomitant with efficient ventilation.[11] Alveolar ventilation as calculated is affected by the tidal volume, respiratory rate, adequate carbon dioxide absorption and adequate perfusion of alveoli with an adequate pO_2. All of these factors must be considered together before determining the efficacy of positive pressure ventilation with or without a negative deflation phase.

SUMMARY

1. Total ventilation, alveolar ventilation, and per cent alveolar ventilation have been studied in anesthetized dogs during spontaneous breathing, during positive pressure endotracheal ventilation, and during ventilation with a tank respirator with the thorax open and with the thorax closed. Both inflation and inflation-deflation pressures were used in the mechanically controlled ventilatory studies.

2. During spontaneous breathing, respiratory acidosis occurred. There was less total ventilation, alveolar ventilation, and per cent alveolar ventilation when compared to mechanically controlled ventilation.

3. The total ventilation, alveolar ventilation, and per cent alveolar ventilation were usually greater except when using the Bennett Assister with the thorax closed, when inflation pressures were used than when inflation-deflation pressures were used.

4. The total ventilation and alveolar ventilation were consistently greater with the Bennett Assister than with the tank respirator, but there was no significant difference in per cent alveolar ventilation.

5. The open thorax had no significant effect except with the Bennett Assister at + 15, 0 mm. Hg when there was significant increase in alveolar ventilation and per cent alveolar ventilation; and with the tank respirator at − 11, + 4 mm. Hg when there was significant decrease in alveolar ventilation and per cent alveolar ventilation.

6. An apparent inefficiency of ventilation which occurred with endotracheal IPP or PNP has been explained by a cyclic flow of gas around the closed anesthesia circuit which registered on the flowmeter but bypassed the lungs (Boyles' Law).

7. In assessing the relative value of a particular method of controlled ventilation during surgery, its effect on cardiac output and venous return must be considered as well as its effect on efficiency and quantity of ventilation.

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MUCO-EPIDERMOID TUMORS OF THE BRONCHUS

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A GROUP of forty-five tumors, principally involving the major salivary glands, was described as a separate entity in 1945 by Stewart, Foote, and Becker.[1] They coined the name, muco-epidermoid tumor, to identify these distinctive lesions, and thought at that time the tumors could, perhaps, be segregated on the basis of histology and clinical behavior, into two categories, malignant and benign. It later became apparent that an occasional benign-appearing tumor did give rise to metastasis, and that the separation was too sharp. It is now their practice to refer to the entire group as malignant, with high-grade and low-grade variants.[2]

It is not surprising that muco-epidermoid tumors occasionally arise in the bronchus since there is great similarity between bronchial glands and the salivary glands of the mouth[3, 4] and since other tumors are common to the two organs. Adenoid cystic carcinoma, commonly referred to as cylindroma, is, perhaps, the best example of a tumor type shared by bronchus and salivary glands. Less frequently encountered tumors common to both sites are the oncocytoma[5, 6] and mixed tumors.[7-9]

A muco-epidermoid adenoma of the bronchus was mentioned by Smetma[10] in his report on an analysis of 100 cases of autopsy of bronchogenic carcinoma in 1952. Also, in 1952, Liebow[11] states that two muco-epidermoid variants of the cylindroid form of bronchial adenoma had been observed at the Armed Forces Institute of Pathology. The same author illustrates an example of a muco-epidermoid carcinoma from the Institute collection. Hellweg and Ricken[8] gave the first detailed report of a benign muco-epidermoid tumor in 1957. The following year, Sniffen, Soutter, and Robbins[12] reported 5 tumors which they thought arose from the surface epithelium of the bronchus. They suggested that their tumors were relatively benign, comparable in activity to the carcinoid adenoma of the bronchus.

We have been interested in muco-epidermoid tumors of the bronchus since we first recognized an example in 1954. Since then we have seen 3 other cases which would seem worthy of comment.

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CASE REPORTS

CASE 1.—A 75-year-old man complained of shortness of breath and bloody sputum for a period of 5 weeks. He had smoked one pack of cigarettes a day for 45 years. Physical examination revealed an emaciated, extremely ill, elderly man. There was dullness to percussion over the right middle lobe area with decreased breath sounds. Roentgen-ray examination of the chest showed an opaque middle lobe. Three sputum examinations were negative for malignant cells. The patient did not respond to antibiotics. His temperature ranged from 100° to 101° F. He died rather suddenly 3 weeks after admission.

Fig. 1.—Case 1. Roentgenogram of chest showing lesion in middle lobe of right lung.

At autopsy the right lung weighed 680 grams; the tracheobronchial tree was filled with fresh blood; the middle lobe of the right lung contained a cavity approximately 7 by 5 cm. Projecting into the cavity was a solid tumor mass, 4.5 by 3 cm. The mass was firm, gray mottled with red, and appeared to arise from the bronchus, 2 cm. from its origin. A careful search failed to reveal metastasis. The microscopic diagnosis was muco-epidermoid tumor. A composite microscopic description will be given subsequently.

CASE 2.—A 59-year-old salesman, complaining of nonproductive cough, chills, and fever, was advised by his physician to remain in bed for 3 months. The prescribed treatment controlled his symptoms and he gained 14 pounds on this regimen. After he returned to work the nonproductive cough returned, but he remained afebrile. Ten months after the onset of symptoms he was admitted to the hospital. X-ray studies of the chest showed a mass in the right superior mediastinum. Bronchoscopy failed to reveal a lesion. At exploratory thoracotomy a 6 cm. mass was found adherent to the upper lobe partially obstructing the

superior vena cava. The mass was separated from the upper lobe and biopsied. The frozen section diagnosis was carcinoma. It was technically impossible to remove the tumor. The permanent sections revealed a muco-epidermoid tumor, high-grade.

CASE 3.—A 61-year-old truck driver was admitted to the hospital with hemoptysis. X-ray examination of the chest revealed a circumscribed mass in the upper lobe of the left lung. After frozen section confirmation of carcinoma, a left pneumonectomy was performed. There was a 4 cm. tumor in the upper lobe, apparently arising from the main bronchus. The cut surface was sticky and mucinous. Multiple hilar lymph nodes were enlarged and replaced by tumor. Permanent sections revealed a muco-epidermoid tumor, high-grade, with regional lymph node metastasis. Three months later he showed signs of deterioration, and a 3 cm. mass became palpable in his liver. He died at home 3½ months after the operation. No autopsy was performed.

CASE 4.—A 52-year-old man sought admission to the hospital because of shortness of breath, cough, and chest pain. X-ray examination of the chest revealed homogeneous consolidation in the region of the middle lobe of the right lung. A bronchogram showed no filling of the bronchus of the middle lobe of the right lung. Bronchoscopy showed a normal orifice to the lobe and failed to reveal a tumor. At exploratory thoracotomy, a mass was found involving the lateral segments of the middle lobe, with scattered pleural implants involving both visceral and parietal pleura, and with metastasis to the lymph nodes in the region of the inferior pulmonary ligament. A biopsy of the pleura was diagnosed as muco-epidermoid tumor, high-grade, metastatic to pleura. The patient was given palliative x-ray therapy of an unknown amount, and received 28 mg. of nitrogen mustard. During the next 4 months he lost considerable weight and developed severe right arm pain and died.

At autopsy the right lung weighed 470 grams. The middle lobe of the right lung was atelectatic. Along the main bronchus there was diffuse neoplastic involvement. Multiple metastatic nodules were present in the other two lobes of the right lung. There were numerous pleural implants and the hilar lymph nodes were replaced by tumor. There was a mass extending from the subcutaneous tissue to the dura; this did not involve the spinal cord, but had completely destroyed spinal processes, six and seven. All neoplastic tissue was gray, honeycombed, and contained sticky, mucoid material. The microscopic appearances of the primary lesion and of the metastatic tumors were similar.

PATHOLOGIC DESCRIPTION

There were no clinical findings which would suggest the diagnosis of muco-epidermoid tumor, nor in any case was the diagnosis suggested by the gross findings. Case 1 had the only low-grade tumor which presented as a circumscribed, but unencapsulated, mass. It was cystic in part, and moderately firm. Foote and Frazell[13] state that about half of the low-grade tumors are cystic, some predominantly so. The other three tumors, all considered high grade, were unencapsulated and showed a honeycombed, mucoid cut surface. This was also true of the metastatic sites.

The microscopic picture was a pleomorphic one. The same three types of cells described in the tumors of the salivary glands[13] were present. The epidermoid portion was most conspicuous in the low-grade tumor. There was actually some keratinization. In the other three cases, mucin-forming cells were the more predominant type, in both the primary and metastatic sites. The mucinous cells lined duct-like spaces, but at times formed rather solid masses. In Case 2 the mucus was predominantly intracellular, whereas in the other cases it was extracellular. There was often coalescence of microcysts forming lakes of mucin with an accompanying inflammatory infiltrate and loss of cellular detail.

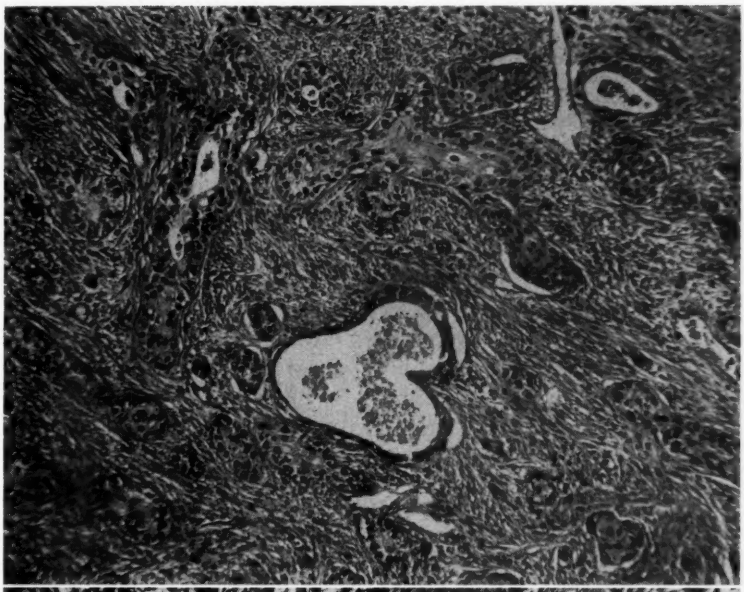

Fig. 2.

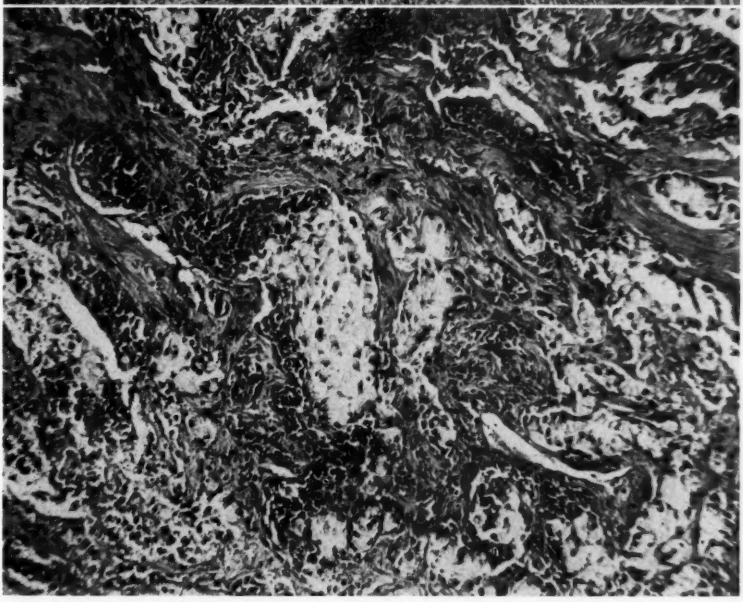

Fig. 3.

Fig. 2.—Case 1. Mucin-forming portion and epidermoid areas are shown. Note the abundant cellular stroma. This was found to be quite characteristic of these pulmonary tumors.

Fig. 3.—Case 2. This tumor featured abundant intracellular mucin.

Fig. 4.

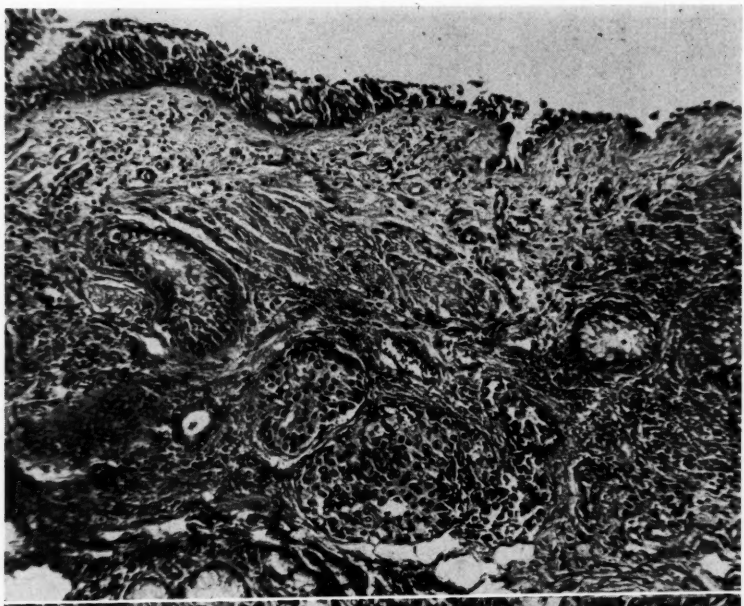

Fig. 5.

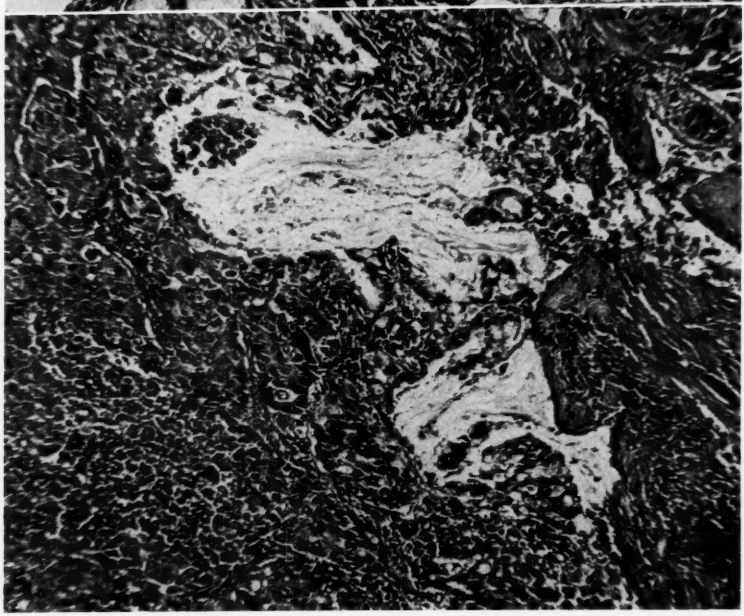

Fig. 4.—Case 3. The tumor is apparently arising from the peribronchial glands. The surface epithelium is intact.

Fig. 5.—Case 3. Large mucus lakes are seen in the deeper areas of this tumor.

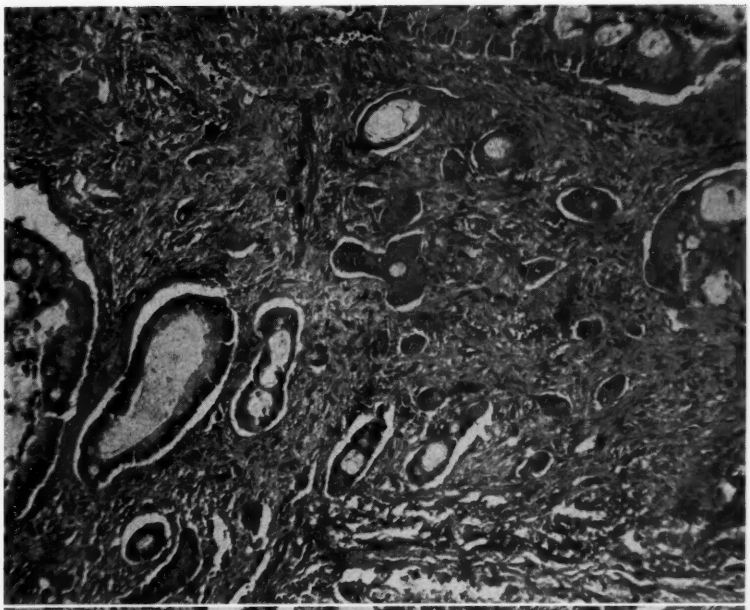

Fig. 6.

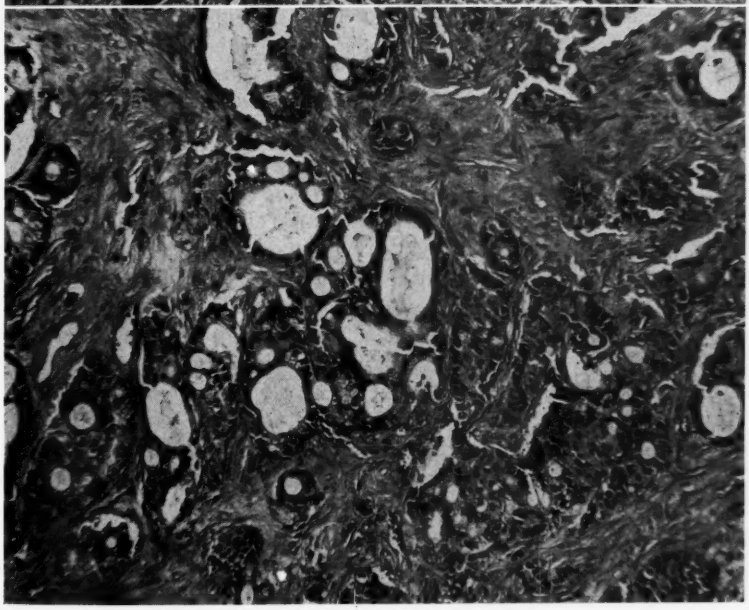

Fig. 7.

Fig. 6.—Case 4. Primary tumor showing cellular stroma.
Fig. 7.—Case 4. Section from metastasis to vertebrae.

All tumors and their metastases stained positively with Mayer's mucicarmine, Alcian blue, and periodic acid–Schiff stains. The intermediate cells were found in varying numbers from tumor to tumor, and in different areas of the same tumor. They were often found in nests or in branching cords immediately adjacent to mucin-forming cells. In 2 of the tumors (Figs. 2, 6, and 7), there was abundant cellular stroma which helped distinguish these tumors from other types of bronchogenic carcinoma. In the other 2 cases the stroma was less conspicuous.

DISCUSSION

With the exception of the case, illustrated by Liebow, from the collection of the Armed Forces Institute of Pathology, the few previously described muco-epidermoid tumors of the bronchus have apparently all been of the "benign," or low-grade variety. The observation of Stewart and of Foote and Frazell that these tumors, when they occur in the salivary glands, are best identified as high-grade or low-grade variants of muco-epidermoid carcinoma would seem also to be true of the bronchial tumors. Three of the 4 cases discussed here were of the high-grade variety, both histologically and clinically. The single tumor which did not spread was similar in appearance to the low-grade tumors found in salivary glands.

The question of origin of these tumors cannot be answered by the scanty material available for study. We did not get the impression that they arose from the surface epithelium in any of the cases we studied. On the other hand, in a single instance, there was morphologic evidence that the tumor did indeed arise from the bronchial glands or ducts. The analogy of these structures to salivary glands would suggest to us that this is the most probable point of origin.

The limited number of cases available for review would not allow for significant clinical observations to be made. The pattern of symptoms, physical findings, and x-ray appearance would not appear to be significantly different from those presented by bronchogenic carcinoma of other varieties, with possibly the exception of rather prolonged symptoms in an occasional instance[12] and a better outlook for long survival in the low-grade variety. Although the tumors are very pleomorphic they are distinctive histologically and similar in all respects to their counterpart in the salivary glands. The metastatic lesions tend to recapitulate the morphology of the primary lesion, and in all cases the three distinct elements were also present in the secondary deposits. One cannot refrain from suggesting that muco-epidermoid tumors are not as uncommon as the sparsity of reports would imply, and that they may not have been identified as a separate group of tumors in past reports on bronchogenic carcinomas. Multiple blocks and specific stains for mucin will facilitate their identification. On the basis that they perhaps do have a better prognosis, and that they may well have a different set of etiological factors involved, it would seem highly worth while to separate them from other types of bronchogenic carcinoma.

SUMMARY

Four cases of muco-epidermoid tumors of the bronchus are presented. Three were of high-grade malignancy and one of the low-grade variety.

The similarity of these tumors to those occurring in the salivary glands is suggested. The need for study of a large group of these tumors to elucidate their natural history is emphasized.

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EXCISION OF RECURRENT CHONDROSARCOMA OF THE RIBS WITH EXTENSIVE INVASION: REPAIR OF THE DEFECTS WITH SURGALOY MESH

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CHONDROSARCOMAS are the most common primary tumor of the ribs. These lesions are usually found in adults and occur twice as often in males as in females. The anterior portion of the upper five ribs is the most common site: 25 per cent of the tumors originate in the first and second ribs. While most authors deem these tumors to be primary lesions, i.e., malignant from their inception, Coley and Higinbotham[1] believed that they start as chondromas or osteochondromas and that malignant changes occur later. They classified the chondroblastic-sarcoma which usually occurs in children and young adults as the primary type. In their series of "secondary" chondrosarcomas observed at the Memorial Hospital in New York from 1931 to 1948 only 4 per cent were found in the ribs.

Reviews of this subject have been published by Hedblom,[2] Sommer and Major,[3] and Dorner and Marcy.[4] The comparative rarity of primary cartilaginous tumors of the rib was evidenced by the number of authors reporting single cases. O'Neal and Ackerman[5] collected 60 cases of malignant tumors of the ribs in a review of the literature. Meyerding[6] stated that approximately 10 per cent of all primary bone tumors occurred in the ribs and sternum. Pascuzzi, Dahlin, and Clagett[7] found only 300 cases of primary tumors of the ribs and sternum reported up to 1957. They recorded 144 cases seen at the Mayo Clinic from 1904 to 1954; 126 occurred in the ribs. Chondrosarcoma constituted 46.5 per cent of the malignant group and 31.7 per cent of all rib tumors. Watkins and Gerard[8] reviewed 339 tumors involving the chest wall observed at the Lahey Clinic from 1938 to 1958. They reported 36 malignant tumors, 7 of which were chondrosarcomas.

Although Graham[9] believed that most of the cartilaginous tumors of the chest wall were malignant, many others considered them benign on the basis of their microscopic appearance. Lichtenstein and Jaffe[10] augmented the criteria for malignancy. Since chondrosarcomas, unlike osteosarcomas, are usually slow

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growing, extirpation is advised. Although invasion of the diaphragm by this tumor has been reported,[3-5, 11-21] there are few references to such extensive involvement of the diaphragm that a prosthesis had to be used. The following case is reported because of the satisfactory result obtained after an extensive excision of a recurrent chondrosarcoma with replacement of the diaphragm, chest wall, and abdominal wall by Surgaloy mesh.

CASE REPORT

The patient, I. G., was a 50-year-old, white woman who was admitted on Dec. 3, 1957, with the complaint of a swelling in the right costal margin of 1 year's duration. Three years previously, the patient entered the hospital because of pain in the right upper quadrant following an attack of "pneumonitis" in the right lower lobe which persisted for 8 months. A mass in the right upper quadrant was found and operation was advised. At operation on Jan. 5, 1955, the mass was found attached to the lower edge of the right rib cage in the anterior axillary line and was densely adherent to the diaphragm. The diaphragm was incised and the tumor was partially removed. The right lobe of the liver was compressed but there was no involvement of the liver by the tumor. The pathologic report at that time read as follows:

> Several large irregular masses of tissue with an aggregate measurement of $17 \times 11 \times 7$ cm. are submitted. Some of these masses are contained within previously ruptured capsules. The greatest portion consists mainly of broken-down nodules of grayish-white, firm, gelatinous tissue and large portions of irregular bony structure. A marked degree of hemorrhage and necrosis is noted. The microscopic sections reveal the tumor to be composed of broad sheets of amorphous and hyaline cartilaginous tissue with scattered, embedded cells. The tumor displays extensive cystic degeneration and large areas of myxoid change and necrosis. A few foci of calcification and bone formation are noted. The bone spicules are unremarkable in appearance and contain mature marrow in the interstices. Cartilage cells are extremely scarce but show variation in size and vacuolar ballooning. Some of the cells contain double nuclei. Considerable nuclear variation with large atypical forms is noted. Mitoses are not found. The diagnosis is chondrosarcoma.

Thirty-six x-ray treatments with a total dose of 7,200 r were given postoperatively. The patient stated that she was well after the operation and was free of pain. She maintained normal activity and gained weight until the present admission. During the 6 months prior to admission, she complained of intermittent discomfort in the region of the mass which increased rapidly in size.

Physical examination revealed an obese, white woman with a mass overlying the ninth to eleventh right ribs in the anterior axillary line. The mass was somewhat cystic, smooth, and slightly tender. It was fixed to the ribs and elevated about 1 inch above the skin level. Distended veins were noted in the skin overlying the mass and the skin appeared to be infiltrated. The liver edge was palpable about 2 inches below the right costal margin. Breath sounds over the base of the right lung were diminished.

X-ray examination of the chest revealed a round shadow about 4 inches in diameter in the lower right peripheral lung field above the diaphragm which was markedly elevated. The intravenous pyelogram revealed the right kidney to be displaced downward and medially (Figs. 1 and 2).

A preoperative diagnosis of recurrent chondrosarcoma of the lower right ribs was made. At operation the tumor, 5 inches in diameter, occupied almost the entire right diaphragm. It infiltrated the lateral wall of the right lobe of the liver and pushed the right kidney downward. The oblique incision extended from close to the midline anteriorly to the erector spinae muscles posteriorly, and circumscribed the involved skin. The fifth intercostal space was entered and the lower seven ribs were divided anteriorly and posteriorly to be removed later with the specimen. The diaphragm was excised completely with the

exception of a small rim posteriorly and around the inferior vena cava. The lower portion of the middle lobe of the lung was attached to the diaphragm and was excised en bloc with the specimen. The lateral abdominal muscles were completely excised together with Gerota's fascia. A portion of the right lobe of the liver was removed but the cleavage plane between the tumor and the liver was not clear-cut. At this point some spillage of grayish-mucoid material occurred. There were numerous small white implants on the parietal pleura which could not be removed. The defect in the diaphragm was replaced by a large piece of Surgaloy (steel) mesh which was sutured to the rim of the diaphragm posteriorly and to the parietal pleura anteriorly and laterally. Another piece of steel mesh

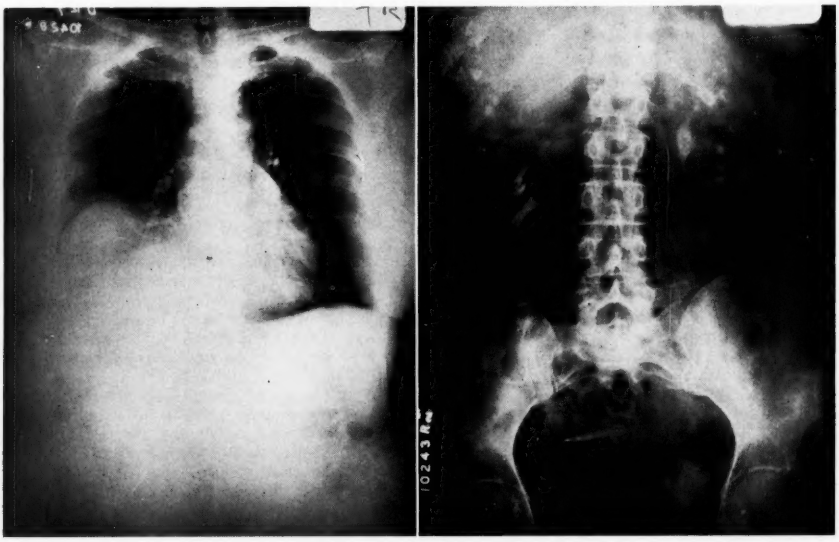

Fig. 1. Fig. 2.

Fig. 1.—Posteroanterior chest roentgenogram which shows round shadow of the tumor above the elevated right diaphragm.

Fig. 2.—Intravenous pyelogram which depicts a mass overlying the eleventh and twelfth ribs, with displacement of the right kidney downward and medially.

was used to bridge the defect in the lateral abdominal wall. This prosthesis was sutured to the lumbodorsal fascia and to the undersurface of the serratus muscle above and to the intercostal bundles between the stumps of the ribs posteriorly. A Bailey catheter was placed in the chest, a sump drain in Morrison's pouch, and two catheters were inserted superficial to the mesh.

The pathologic examination revealed numerous thick-walled, fluctuant, spherical cysts, ranging from 2 to 7 cm. in diameter. All of the cysts were attached to the intercostal muscles and were present in the deeper portions of the attached segment of skin, subcutaneous tissue, diaphragm, and within the substance of the attached segment of liver. Some of the cysts were filled with thick, "egg-white" material while others were filled with hemorrhagic debris. The microscopic examination revealed irregular lobules of cartilaginous cells which showed marked nuclear variation. The cells were separated by wide zones of granular, faintly basophilic, material. The lobules were separated by wide bands of fibrous and hyaline tissues. No definite tumor capsule was noted. The tumor infiltrated the fatty and soft tissue and was present in sections taken from the liver, lung, diaphragm, and the fatty tissue labeled omentum. The diagnosis was chondrosarcoma.

The postoperative course was uneventful except for an elevation of temperature to 101° F. during the first 3 days after surgery. All drains were removed by the fifteenth postoperative day. Thrombophlebitis in the left leg was observed on the eleventh postoperative day when heparin therapy was started. Twenty-seven days after operation, 200 c.c. of clear amber-colored, sterile fluid, superficial to the abdominal steel mesh, was aspirated. The patient was discharged on the thirty-first postoperative day. She has been seen at intervals of 3 to 6 months since discharge from the hospital. She is busily engaged in her housework and continues to be overweight. There is no pain except an occasional "drawing" sensation in the incision in damp weather. At the last examination on April 26, 1960, more than 2 years after the operation, the patient was overweight. The incision was well healed with no evidence of hernia. No masses could be felt. The liver was not enlarged. The lungs were fully expanded. On fluoroscopy, both chest wall and diaphragmatic prostheses revealed no paradoxical movement (Fig. 3).

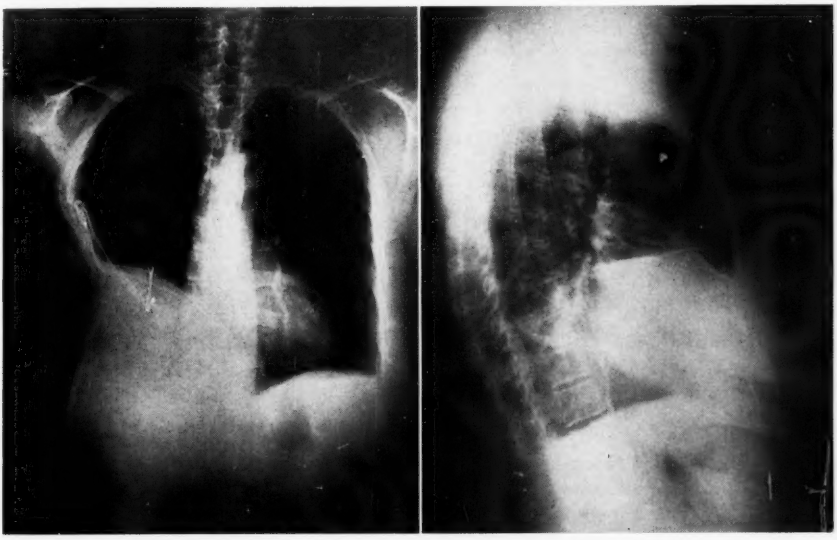

Fig. 3.—Postoperative posteroanterior and right lateral chest roentgenogram which shows steel mesh prostheses of the chest wall, diaphragm, and abdominal wall.

DISCUSSION

The clinical course associated with a chondrosarcoma is usually insidious and protracted. Wide extirpation of the primary tumor is the treatment of choice. A high rate of recurrence occurs if the tumor is entered or incompletely excised. The recurrent tumors may still be amenable to excision. Pascuzzi and associates[7] reported 2 cases with survivals of more than 6 and 9 years after many resections for recurrent chondrosarcoma. Our patient had had a previous limited excision of a chondrosarcoma of the lower right ribs 3 years prior to this admission. The second operation consisted of a wide excision of the lower seven ribs, the lateral abdominal wall, about 95 per cent of the right diaphragm, and a large portion of the right lobe of the liver. Prostheses had to be employed to bridge the defects.

Different kinds of material have been used to repair tissue defects. Defects in the chest wall or diaphragm pose a special problem because of the respiratory movements. Fascia lata was used by Watson and James[19] and Clough.[16] The transversus abdominis and the latissimus dorsi muscles were employed by Rives and Baker,[22] Chisholm[23] and Campbell.[24] Geever and Merendino[25] employed cutis grafts in the dog to bridge small defects but, when the defect was large, paradoxical motion of the chest wall and of the diaphragm occurred. Beardsley[26] used a tantalum plate as a prosthesis to eliminate paradoxical motion of the chest wall. Its impermeability, although perforated, was associated with a serous collection and infection which necessitated its removal. Tantalum mesh was widely used because of its strength, inertness, flexibility, and permeability. It was employed by Ada and Hevenor,[27] Sanford,[28] Effler,[29] Beardsley and Cavanagh,[30] and Cotton and co-workers.[20] However, tantalum mesh, despite the abundant deposition of fibrous tissue, tends to fragment and, in three instances reported by Adler and Firme,[31] herniation through the fragmented tantalum mesh took place. Stainless steel mesh had been used by Effler[29] and Cotton and his colleagues[20] with good results and it was employed successfully in this case. It is strong enough to act as a suitable strut and to prevent the paradoxical motion of the chest wall and diaphragm. On the other hand, it is flexible enough to conform to the physiologic movement of the thorax. It is inert and permeable. It is superior to tantalum mesh because it can withstand shearing stress, displays less degree of fatigability, and does not fragment.

During the past few years, many synthetic materials have been tried: nylon by Adler and Firme[32]; Ivalon sponge by Harrison,[33] Blumberg[34] and Haupt[35]; Teflon by Harrison[36]; and a polyethylene ester, Marlex, by Usher and his associates.[37-40]

Nylon loses its tensile strength in the body because of its hydrophilic properties and basic chemical structure. Ivalon sponge excites an extreme degree of foreign body reaction with subsequent shrinkage. Calcification may occur within the interstices of this prosthesis. The other synthetic meshes or nets proved useful because they retain their strength in the body even in the presence of infection. They are inert, pliable, permeable, and not as rigid as metallic mesh which, in some instances, has projected through the skin or eroded adjacent blood vessels. According to Graham and his co-workers,[40] paradoxical motion disappears within a few days after the insertion of Marlex. Under these circumstances this mesh should prove to be a most desirable prosthesis.

SUMMARY

A recurrent chondrosarcoma excised with wide resection of the chest wall, the abdominal wall, 95 per cent of the right diaphragm, and a portion of lung and liver has been described. The defects in the chest wall and the diaphragm were replaced with separate sheets of stainless steel mesh. Two years after the operation the patient is free of disease and shows no paradoxical motion or herniation.

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KARTAGENER'S SYNDROME

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KARTAGENER'S syndrome is characterized by the triple association of situs inversus, bronchiectasis, and sinusitis. Although Kartagener was not the first to report this condition, he was the first to interpret and correlate the combination of findings as something more than chance association.

Many authors have reviewed the available literature and presented cases; some favor congenital and acquired etiology rather than the congenital origin explained by Kartagener. His first report in 1933 described a group of patients with bronchiectasis, dextrocardia, and congenital absence of the frontal paranasal sinuses. Nearly half of these patients had symptoms of cough in the first decade of life and one fourth developed symptoms in the next 10 years. In 1937, Adams and Churchill[1] noted that bronchiectasis in this type of patient had the characteristics of being an acquired condition. In 1949, Churchill reiterated his belief that bronchiectasis is probably acquired secondarily in Kartagener's syndrome rather than being a truly congenital condition. The congenital nature of bronchiectasis is difficult to prove anatomically because findings are comparable to the ordinary acquired type. However, most authors agree that a congenital process plays an important role in the etiology of this syndrome.

According to Olsen[7], 85 cases of total visceral transposition were observed at the Mayo Clinic in 22 years, 14 of these patients had bronchiectasis and abnormal sinuses; 10 of the 14 had nasal polyposis. Bronchiectasis occurred in 0.5 per cent of total patients registered and in 16.5 per cent of patients with situs inversus. A congenital factor was favored in the face of this statistical confirmation.

Torgenson[7] reported 14 cases of Kartagener's triad in 129 visceral transpositions (123 of which were total), accompanied by nasal polyposis in 8 per cent. He also cited the coincidence of situs inversus and bronchiectasis in several members of a family as a further argument for a common congenital origin.

In situs inversus, a striking malformation occurs transposing organs as in a mirror image, right for left and left for right. All of the internal organs may be reversed; however, transposition of the thoracic or abdominal viscera alone may occur. Although the cause is unknown, this reversal is part of

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the mechanism whereby bilateral symmetry and asymmetry are normally established. It has been stated that an activity gradient is present between the two halves of the embryo in the production of bilateral asymmetry. According to Arey's *Developmental Anatomy,* a determining factor for the asymmetries of the viscera can be shown to lie in the gut of amphibians, since a 180 degree rotation of the archenteron roof that corresponds to the later duodenum brings about situs inversus. Transposition of the viscera is an extreme type of symmetry reversal; however, left-handedness and counterclockwise hair whorl are milder evidences of this tendency.

Dr. Howard Lilienthal of New York in a comment on this subject objected to the term "reversal of symmetry." He believed that something symmetrical cannot be reversed and prefers to call it reversal of normal asymmetry in dealing with human beings.

As early as 1887, George Fisher[1] wrote that congenital transposition of viscera is a variation from the normal type of animal organization. He referred to the science of teratology, a part of the broader field of normal embryology, in stating that nearly all malformations are the result of arrest of development at some stage of embryonic growth.

Available embryologic data make tenable the hypothesis that two types of individuals with transposition of viscera may exist, the first type being normal mutants and the second being true monsters in whom other stigmata of maldevelopment may be expected. Regarding Kartagener's syndrome, the inference to be drawn is that bronchiectasis in these cases is to be considered as a sign of maldevelopment.

CASE REPORT

An 18-year-old man was first examined on Oct. 5, 1955, for a productive cough of several years' duration. The sputum was foul, thick, and yellow in appearance. The patient estimated that approximately 10 teaspoonsful per day were evacuated from the tracheobronchial tree. Other generalized complaints were ease of fatigue, weakness, fever, and a weight loss of approximately 10 pounds during the past year. The patient was subject to frequent respiratory infections. Complaints of nose bleeding and a postnasal drip were also present. There was a childhood history of whooping cough, measles, and chicken pox. The patient's birth was uncomplicated.

Physical examination revealed a thin, white man with the apex beat of the heart at the fifth interspace about 7 cm. from the mid-sternal line on the right side. Otherwise, there was no evidence of a cardiac abnormality. Breath sounds on the right side were normal; however, on the left side decreased sounds anteriorly and laterally as well as musical and moist râles were present. There was no evidence of cyanosis or clubbing. In the right nostril there was a polypoid-like lesion and inflammatory changes. The chest roentgenogram revealed dextrocardia and a triangular area of increased density in the region of the middle lobe on the left side consistent with an atelectatic area as well as pneumonitis and the possibility of bronchiectasis. The diaphragm was elevated somewhat more on the left side than on the right, and an air bubble in the stomach was seen on the patient's right side suggesting a situs inversus totalis. Bronchoscopy disclosed inflammatory changes involving the mucosa and thick yellow secretions, especially on the left side. No other abnormality was evident, except that individual bronchial orifices to middle lobes on the right and left sides were present. Bronchography revealed three distinct lobes on both the right and left sides.

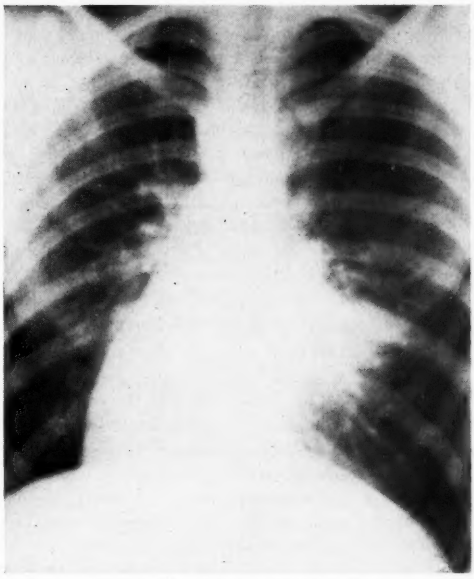

Fig. 1.—Plain roentgenogram of the chest on Oct. 5, 1955, reveals the dextrocardia. An air bubble was also present in the stomach on the right suggesting a complete situs inversus. A diffuse fanlike infiltration extends outward from the left hilum.

Fig. 2.—A left lateral view of the chest after the introduction of contrast medium reveals extensive bronchiectasis involving the anterior segment of the left upper lobe, the entire middle lobe, and the basilar segments of the lower lobe.

The right lung showed no evidence of abnormality involving the bronchial structures. On the left side, saccular bronchiectasis involved the basilar segments of the lower lobe, the entire middle lobe and the peripheral portion of the anterior segment of the upper lobe.

Operation.—A left thoracotomy was performed on November 25, at the Good Samaritan Hospital, Lexington, Kentucky. Resection included the segments involved by bronchiectasis, namely, the anterior segment of the upper lobe in conjunction with the middle lobe and also the basilar divisions of the lower lobe, however, the superior dorsal segment was allowed to remain in place inasmuch as it was not diseased. The middle lobe was as severely involved as had been conjectured by the bronchogram and plain roentgenogram. There was an independent bronchial division to the middle lobe; but there was no evidence of a horizontal fissure between the middle and upper lobes. The middle lobe was of the consistency of liver and, being very friable, was separated from the upper lobe with difficulty. This patient was last examined on March 29, 1960, at which time there was no complaint referable to the respiratory system and x-ray examination of the chest revealed no evidence of infiltration in either lung field.

Bronchiectasis in Sister.—This 11-year-old girl was a sister of the above patient and her complaints referable to respiratory illness were similar to the history as given by her brother, namely, productive cough with weakness and failure to gain weight. She likewise was subject to very frequent respiratory infections. Bronchoscopy revealed thick secretions within the orifice of the right middle lobe, and the absence of filling of the middle lobe by bronchography. Following specific drug therapy and expectorants for 1 month, the bronchogram revealed good filling of the bronchial tree with evidence of extensive saccular bronchiectasis involving the entire right middle lobe. At operation the middle lobe was firm, atelectatic, and of a dark red appearance. The weight of the resected lobe was 40 grams. The diagnosis by the pathologist was chronic nonspecific pneumonitis and saccular bronchiectasis. When last examined on June 24, 1960, the patient's status referable to the respiratory system was considerably improved.

SUMMARY

A case of Kartagener's syndrome is presented, as well as a summary of the patient's 11-year-old sister who had evidence of extensive saccular bronchiectasis which required a right middle lobectomy. This author believes that the familial association and age of the sister once again confirm the congenital nature of bronchiectasis in Kartagener's triad.

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AN EXPERIMENTAL STUDY OF PLEURAL SYMPHYSIS

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THE high incidence of spontaneous pneumothorax has recently become more evident in the medical observation of young men in the armed forces. A significant number of these cases go on to chronicity or recurrence. The published incidence of recurrence has been reported between 2 and 45 per cent and is probably closest to 25 per cent.[1, 3, 5, 15]

Over 50 years ago it was noted that in patients who developed acute pleuritis in the presence of chronic pneumothorax the lung often re-expanded. Chemical and mechanical agents have been instilled into the pleural space to induce pleuritis. The resultant inflammatory reaction is thought to seal the pleural leak and, when the lung is fully expanded, it obliterates the pleural space.

A large number of agents have been used for this purpose, including talc,[6, 10, 12] kaolin,[9] hypertonic glucose,[2] iodized poppy-seed oil (Lipiodol),[2] gemonil in oil, turpentine, streptokinase-streptodornase,[11] silver nitrate,[1] iodoform, and autogenous blood.

This study was undertaken in order to evaluate the type of adhesion produced by some of these procedures, the protection afforded by the procedure, and the effect on the underlying lung.

METHOD

Four methods of producing pleural symphysis were studied. Twenty-four unselected mongrel dogs were divided into the following groups:

Group I.—Five dogs were subjected to a standard thoracotomy through the fifth intercostal space. Five grams of sterile powdered talc were rubbed onto the costal parietal pleura from the apex of the thorax to the diaphragm and over the lateral surface of the lung. The talc was left in the pleural space and the chest was closed in layers. Residual intrathoracic air was aspirated through an indwelling chest tube which was removed about 3 hours after the completion of the operation.

Group II.—Six dogs had 20 ml. of warmed iodized poppy-seed oil (Lipiodol) instilled into the pleural space after standard thoracotomy. Ten milliliters were applied smoothly to the exposed pleural surfaces with the chest open and the second 10 ml. of oil was injected via an indwelling chest catheter after closure of the chest and removal of intrapleural air.

Group III.—Six dogs had 10 drops of 10 per cent silver nitrate solution applied to the lateral visceral pleura after standard thoracotomy and closure as above.

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Group IV.—Seven dogs had thoracotomy and parietal pleurectomy performed. The parietal pleura was dissected from the endothoracic fascia over the costal surface from the dome of the thorax to the seventh rib and from the anterior midline to the mediastinal reflection posteriorly. Closure of the chest was as described above. All agents were applied via open thoracotomy in order to be comparable with the pleurectomy group.

These animals were then studied 3 to 4 months later. Under light pentobarbital anesthesia an attempt was made to induce pneumothorax by placing 18-gauge needles into the chest through the second and seventh intercostal spaces, to a depth at which a free flow of air was obtained. Upright posteroanterior radiographs of the chest were made with the needles in place in order to note the degree of pneumothorax induced.

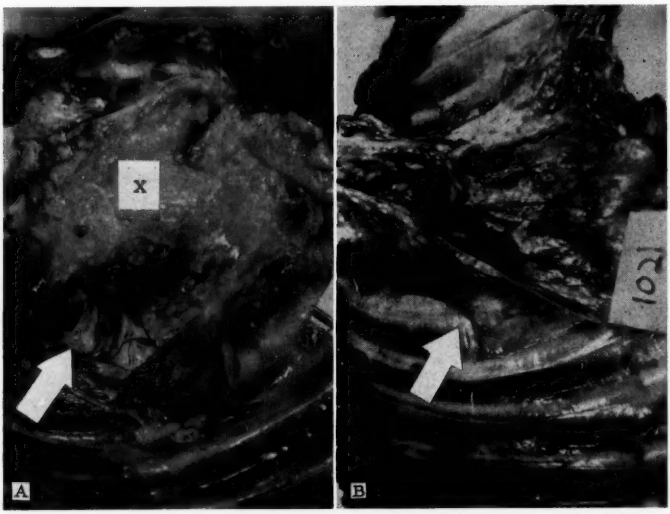

Fig. 1.—*A*, Hemithorax and adherent lung of talc-treated dog (No. 199). Note that the lung is plastered to the chest wall and encased in dense white fibrous tissue *(X)*. The transected main bronchus can be seen at the lower left-hand corner of the photograph *(arrow)*.

B, Hemithorax and adherent lung of dog treated with parietal pleurectomy (No. 1021). The main bronchus is seen at the center of the photograph. The lower border of the lung is reflected upward demonstrating the nature of the adhesions *(arrow)*.

The contralateral thorax was used as a control in each animal. Some of the animals had had an incidental thoracotomy produced in the contralateral thorax at least 3 months prior to this experiment.

Finally, each animal was sacrificed and the chest examined. Appropriate segments of adherent lung were preserved for histologic study.

RESULTS

The individual results are tabulated in Table I.

It should be noted that the radiographs of the chest were difficult to evaluate in many instances because of the narrow configuration of the dog's chest.

Talc.—None of the talc-treated animals exhibited any respiratory distress when needles were placed into the treated side. Radiographic examination of these treated sides showed minimal or no pneumothorax in every case. Postmortem examination uniformly revealed very dense, thick, diffuse adhesion

between the lung and chest wall with practically no remaining pleural space. Dense adhesions were also found between the lobes and to the mediastinum. The lung appeared to be encased in dense fibrous tissue, and sometimes appeared compressed by it. It was impossible to create a plane between the lung and chest wall without tearing parenchyma. Microscopic examination revealed dense fibrous tissue with foreign body giant-cell granulomata and moderate infiltration by macrophages, lymphocytes, and polymorphonuclear leukocytes. Aside from a narrow zone of relative atelectasis adjacent to the fibrosis, the underlying lung parenchyma appeared normal. One animal (No. 940) had a chronic emphyema cavity containing about 100 c.c. of purulent material. In 2 animals, serial films showed pleural effusion during the second and third weeks after treatment which was not present after 3 months.

Lipiodol.—Of the 6 Lipiodol-treated animals, only 2 had significant protection from pneumothorax. Half these animals had no adhesions ascribable to the oil, and the fourth had only a few filmy, easily lysed, fibrous adhesions between the lung and chest wall. The remaining 2 animals surprisingly had rather diffuse adhesions, which were, however, considerably less dense than those in the talc group. Histologically, the adhesions were not remarkable. The underlying lung appeared completely normal except for 1 animal (No. 1454) which had pneumonia and atelectasis in a small segment of adherent lung. Lipiodol was identifiable on all the radiographs several months after instillation.

Silver Nitrate.—Similarly, the animals treated with silver nitrate were poorly protected from pneumothorax. The adhesions in these animals were found to be few and irregularly scattered, with a haphazard distribution. Most of these adhesions could be easily broken with the finger without tearing lung parenchyma. Microscopically, there was no damage to underlying lung, and these specimens could not be differentiated from the group treated with Lipiodol. These animals had pleural fluid demonstrated on a 48-hour film, but the fluid had resolved 9 days after the procedure.

Pleurectomy.—All the animals treated by partial parietal pleurectomy showed moderately good protection from pneumothorax. When pneumothorax was radiographically identified, the amount of collapse was estimated to be 15 per cent or less in all instances. The adhesions in these animals were moderately dense; less so than in the group treated with talc but more dense than in the groups treated with silver nitrate or iodized oil. The adherent areas were confluent and diffuse. Most of the animals had patches of lung uninvolved by adhesions (Fig. 1, *B*). In this group, also, there was no microscopic evidence of damage to the underlying lung.

Several dogs died in the immediate postoperative period and were not included in the groups just reported. Two of these were the first dogs treated with silver nitrate in which 30 c.c. of 1 per cent solution was used. After an uneventful thoracotomy, both these animals failed to recover spontaneous

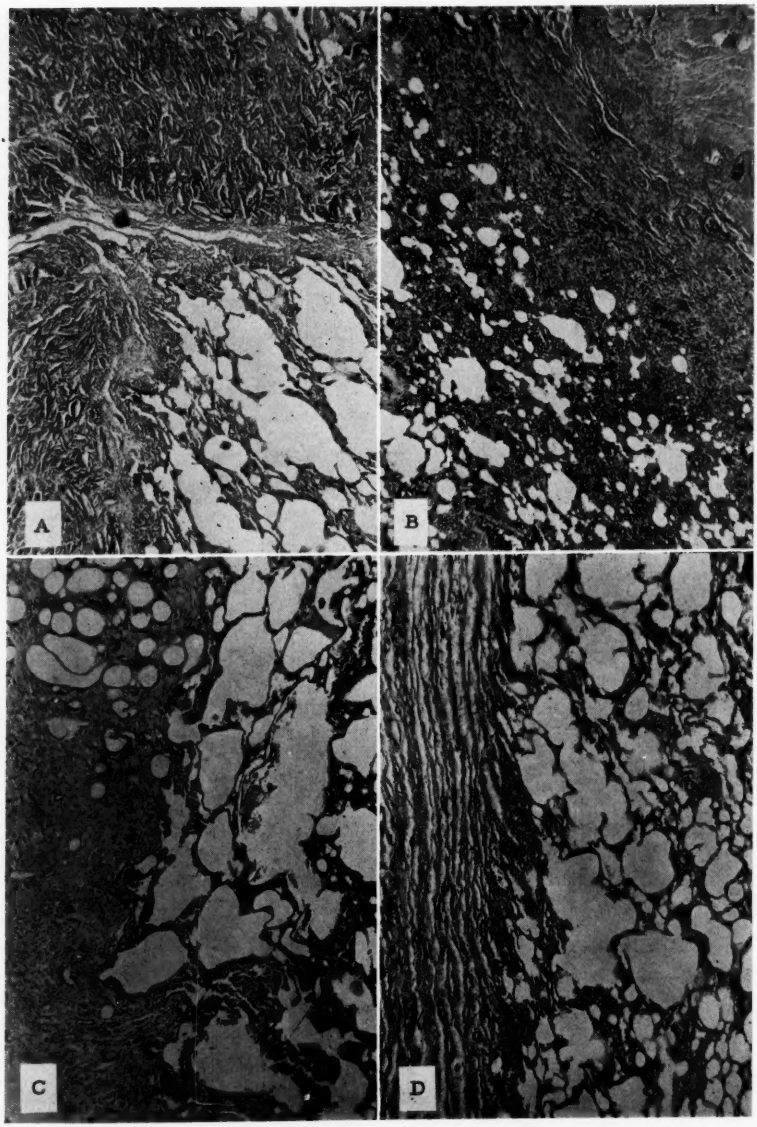

Fig. 2.—Photomicrographs (×58; reduced ¼).

A, Section from junction of lung and adjacent fibrous tissue after talc-induced pleural symphysis. The lung is seen at the lower right corner. The surrounding fibrous tissue consists of numerous ovoid talc granules, giant cell reaction, and dense connective tissue. (See Fig. 3.)

B, Lung and adjacent fibrous reaction after parietal pleurectomy. The connective tissue is moderately dense. The dark spots are pigment-containing macrophages.

C, Lung and adjacent fibrous reaction after Lipiodol-induced pleural symphysis. The Lipiodol oil globules are seen at the left upper corner of the photograph.

D.—Lung and adjacent fibrous reaction after silver nitrate-induced pleural symphysis. The lung tissue was normal in all these specimens.

respirations when removed from the automatic respirator. The toxic manifestation of silver nitrate when absorbed systemically is depression of the respiratory center,[16] which was apparently the mechanism here.

One animal who underwent parietal pleurectomy died on the third postoperative day and was found to have a considerable amount of free blood in the thoracic cavity.

In summary, we have found that the chemical irritants, silver nitrate and iodized poppy seed oil, usually produce only scattered filmy adhesions. Satisfactory pleural symphysis is rarely and inconsistently produced.

Intrapleural talc produces the most marked pleural irritation and creates the most homogeneous and dense adhesions, sometimes encasing the lung in fibrosis.

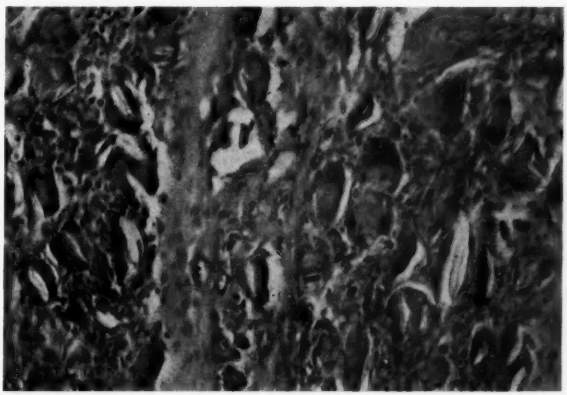

Fig. 3.—High-power view of talc-induced fibrosis demonstrating the talc granules (ovoid clefts), giant cell reaction, and dense connective tissue (×150; reduced ¼).

Parietal pleurectomy produced fairly diffuse, moderately dense adhesion between lung and chest wall which could be separated by sharp dissection.

None of these techniques produced significant damage to underlying lung tissue.

DISCUSSION

The proper treatment of chronic and recurrent pneumothorax has received a great deal of attention in the surgical and medical literature and still remains debatable.

The great majority of surgeons favor operative intervention because of the high incidence of demonstrable underlying pulmonary lesions which lend themselves to specific resectional therapy.[4, 5, 8, 14, 15, 17, 18]

When pneumothorax becomes chronic, usually some mechanical cause can be found which maintains the bronchopleural communication.[4, 5, 8, 15] This may be due to epithelization of a previously established bronchopleural fistula or rupture of a bulla or cyst which has a large bronchial communication. Often

TABLE I

DOG	TIME INTERVAL (MONTHS)	CLINICAL REACTION TO INDUCED PNEUMOTHORAX		RESULTS OF INDUCED PLEURAL SYMPHYSIS			
				RADIOGRAPHIC FINDINGS*			
		TREATED	CONTROL	TREATED	CONTROL	GROSS FINDINGS	MICROSCOPIC FINDINGS
				Induced With Talc			
199†	3	0	+‡	0	++++	Extremely dense adhesions between all lung surfaces, chest wall, and mediastinum	Dense fibrous tissue, talc granulomata, giant cell and polymorphonuclear reaction, narrow rim of compressed lung
200†	3	0		+	+	As above	As above
1252	4	0	+	0	+	As above, scattered adhesions on the opposite side	As above
1340	4	0	0	0	0	As above	As above
940	4	0	+	Cloudy	+++	Large empyema cavity; lung compressed and encased in reaction	Acute inflammatory exudate; atelectasis
				Induced With Lipiodol			
65†	3	+	+	+++	+++	Adhesions only to operative scar, none due to lipiodol	Mild fibrosis, macrophage and round cell infilbration; normal underlying lung
644†	3	+	+	+++	+++	As above	As above
1448	3	No data		+	+	As above	As above
1454	2	Killed by another animal prior to study				No adhesions	Areas of pneumonia and atelectasis; very little fibrosis
967	3	0	+	0	++++	Diffuse adhesions to chest wall and mediastinum	Moderate fibrosis, oil spots noted, normal underlying lung
934	4	0	+	+	++++	Strong adhesions of upper and middle lobes to chest wall	As above but no oil spots seen
				Induced With Silver Nitrate			
60†	3	+	+	++	++++	A few interlobar adhesions, otherwise lung was free	Moderate vascularized fibrosis, pigment containing macrophages, underlying lung normal

53†	3	+	0	+	++	Scattered filmy adhesions, easily lysed	As above
936	4	+	+	+++	+++	As above	As above
969	4	+	+	+++	++++	As above	As above
1343	3	+	+	++	++++	As above	As above
1295	3	0	0	+	++	Moderately dense scattered adhesions of upper lobe to chest wall, remainder free	As above
				Induced With Partial Pleurectomy			
764	3	0	+	+	+++	Dense fibrous shell over upper ⅔ of lung, large areas of atelectasis	Dense vascularized fibrous tissue, pigment containing macrophages, areas of atelectasis
941	4	0	+	+	++	Upper and middle lobe completely adherent to chest wall, strips easily	Moderate fibrosis, intra-alveolar hemorrhage
576†	3	0	0	0	+	Diffusely scattered moderately dense adhesions	Moderate fibrosis, pigment containing macrophages, scattered polymorphonuclear leukocyte clusters
950	4	0	+	0	++++	Entire lung diffusely adherent to chest wall	Moderate fibrosis, mild poly and round cell infiltration, underlying lung normal
1021	3	0	+	+	++++	Almost entire lateral lung adherent to chest wall, plane of dissection can be found	Moderate fibrosis, round cell infiltration, narrow zone of lung compression, remaining lung is normal
1412	3	0	+	+	++	As above	As above
1342	3	Data not available				As above	As above

*0 indicates no observable pneumothorax. + indicates approximately 0 to 25% pneumothorax. ++ indicates approximately 25 to 50% pneumothorax. +++ indicates approximately 50 to 75% pneumothorax. ++++ indicates approximately 75 to 100% pneumothorax.

†After dog number indicates that the animal had had a thoracotomy previously on the control side.

‡+ under "Clinical Reaction" indicates respiratory distress as manifested by gasping, tachypnea, and cyanosis at the time of the needle-induced pneumothorax.

an adhesive band near a pleural tear prevents collapse of this area and keeps the leak open. In those cases in which collapse of the lung is followed by exudation, a thickened pleural membrane may form which prevents re-expansion of the lung. These situations are amenable to surgical correction.

Frequently, however, even though the primary defect is repaired, diffuse pulmonary disease, such as bullous emphysema, makes pleural symphysis desirable in order to prevent recurrence. Both parietal pleurectomy and talc poudrage have been used in these instances.

Other physicians have advocated nonsurgical pleural symphysis by needle or thoracoscopic instillation of chemical or mechanical irritants, particularly in cases in which there are medical contraindications to surgery or when the disease is clearly too diffuse for local resection. Silver nitrate and iodized poppy-seed oil have probably been used most often for this purpose.

On the basis of this work, we agree with Gaensler[15] that closed pleural symphysis with chemical agents is very uncertain and frequently useless. The production of a few scattered adhesions as induced by silver nitrate or Lipiodol is more likely to support chronicity than to improve it. Furthermore, these techniques are not without serious morbidity because of the intense chemical pleuritis. Frequently, multiple treatments are necessary, producing a prolonged hospital stay in excess of that after operation.

Both pleurectomy and talc poudrage appear to give satisfactory pleural symphysis. The talc produces an intense fibrosis, which is somewhat more violent than desired. However, both techniques have been used clinically with success, and both have been shown to produce only mild reduction of pulmonary function in the immediate postoperative period which subsequently returns to normal.[6, 7, 15]

Both procedures can be associated with serious complications.[15, 17] Pleurectomy may be associated with intrathoracic bleeding which may go on to form a restrictive pleural membrane and fibrothorax. Horner's syndrome has been described after apical pleurectomy. These complications can be averted by careful dissection and hemostasis.

Poudrage also may be followed by persistent exudation and its sequelae. Embolus with hemiplegia has been reported after the instillation of talc.

In view of the available evidence, we favor open thoracotomy, indicated resectional therapy, and parietal pleurectomy with underwater suction drainage as the correct treatment of chronic and recurrent pneumothorax.

Chemical pleural symphysis should be reserved for those instances in which operation is definitely not feasible.

SUMMARY

This study was undertaken to evaluate several modes of producing pleural symphysis. Silver nitrate, iodized poppy-seed oil (Lipiodol), and talc instilled into the pleural space of dogs were compared with parietal pleurectomy. The first two chemical irritants produced only scattered adhesions and pleural symphysis was unsatisfactory.

Intrapleural talc and pleurectomy produced satisfactory pleural symphysis. In the case of talc, the adhesions were more dense than is desirable.

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A SIMPLE TECHNIQUE FOR ASSISTED-CONTROLLED ANESTHESIA IN DOGS

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THERE is an urgent need for a simple reliable method of administering assisted-controlled anesthesia to laboratory animals. This is especially exigent in the average experimental surgery laboratory where intrathoracic operations are performed without the services of an experienced anesthetist. It is our endeavor to present a method of obtaining a smooth, light, assisted-controlled anesthesia that can be administered by the average intern, resident, animal caretaker, or even a member of the operating team if the occasion arises.

EQUIPMENT

Various types of respirators have been recommended for dog surgery by Miller,[1] Lewis,[2] Zuidema, Clarke, and Smith,[3] Smith[4] and others, none of which have the assistor feature. Saklad, Saklad, and Cox[5] have recently performed physiologic studies with four pressure breathing apparatuses including two assistors, all of which lack many desirable features of the respirator used in our experiments.

This assistor-controller (Bird-Mark 7 respirator) is compact (5 by 5 by 11 inches) and attaches directly to the reducing valve on an oxygen tank. Fig. 1 illustrates the following features: a nebulizer to supply a low surface tension mist to the lower respiratory tract if desired (*A*); a pressure regulator to control the pressure in the bronchi and lungs (*B*); an air mix pull which will deliver 100 per cent oxygen when in, and a 40 per cent oxygen and 60 per cent room air when pulled out (*C*) (this economy factor will decrease the oxygen consumption 4 times); an auto-timer to regulate the respiratory rate when the chest is open or the animal apneic (*D*); a sensitivity control which holds the inflow valve in a closed position during exhalation and periods of rest between breathing excursions (*E*) (it is set to correspond with the respiratory efforts of the dog and when the chest is open or the animal apneic it is set for minimum effort); a hand timer for manually controlling respirations or in pre-setting pressures (*F*); a flow rate valve which will regulate the length of inspiration (*G*); an exhalation valve below the nebulizer and near the animal to keep dead space at a minimum (*H*).

TECHNIQUE

A healthy animal is a fundamental prerequisite. All of our dogs come from the city pound and are universally infested with a variety of worms

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and fleas. They are immediately bathed, dipped in a pesticide, dewormed, debarked, and given rabies and distemper vaccine. Following these procedures they are kept in clean pens with runways for 10 to 14 days. If they eat well and appear healthy they are moved to dog cages adjoining the operating room and prepared for surgery.

Solid food is withheld for 12 hours before operation and no premedication is administered. Immediately before operation the dog is led outside to the nearest tree and with a little patience he may defecate as well as urinate, both of which avoid a mess in the operating room.

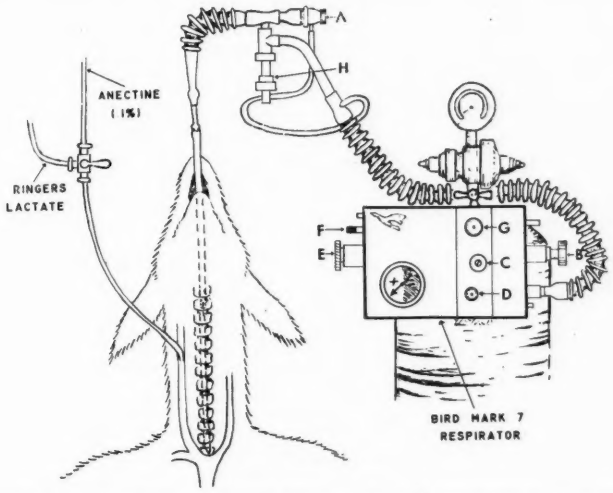

Fig. 1.—The anesthesia "set-up" with the Bird-Mark 7 controller-assistor respirator and its component parts: *A*, nebulizer; *B*, pressure regulator; *C*, air mix control; *D*, auto-timer; *E*, sensitivity control; *F*, hand timer; *G*, flow rate valve; and *H*, exhalation valve.

The dog is then muzzled, placed on the operating table, and a venipuncture performed in the radial vein of one of the anterior legs. A 0.5 per cent solution of Pentothal sodium is allowed to drip until the animal is stuporous, at which time this solution is discontinued and a 0.1 per cent solution of succinylcholine chloride allowed to drip until the dog is relaxed but not apneic. A cuffed endotracheal tube is quickly inserted and connected to the Bird-Mark 7 respirator. The sensitivity is regulated to assist the dog's respirations and the ratio of inspiration to expiration set at 1 to 3. A pressure of 10 to 15 cm. of water provides adequate ventilation with a closed chest. The anterior jugular vein is next cannulated and connected to a three-way stopcock with a solution of Ringer's lactate on one side and a 0.1 per cent solution of succinylcholine chloride on the other. A four-way stopcock may be used if the venous pressure is monitored. The entire "set-up" is illustrated in Fig. 1, which shows the controls well within reach of the surgeon or his assistant.

The dog is prepared and draped and the operation proceeds with a slow drip of Ringer's lactate going into the jugular vein. If the animal becomes too light the anesthetist or a member of the operating team simply turns the

three-way stopcock and allows a small amount of the 0.1 per cent succinylcholine solution to go into the jugular vein. When the animal is again relaxed, the stopcock is returned to the Ringer's lactate drip. If deeper anesthesia is desired, the 0.5 per cent solution of Pentothal sodium is reintroduced into the system and allowed to drip slowly until the required plane is reached.

If the thoracic cavity is opened or the dog becomes apneic, the respirator is equipped with an apnea or auto-timer valve that will take over control of the anesthesia at the desired rate. Usually 15 to 20 respirations per minute with a 1 to 2 ratio of inspiration to expiration will ensure proper ventilation. A pressure of 15 to 20 cm. of water is required to keep the lungs well inflated while the chest is open. When the chest is closed the respirations are controlled until the animal has sufficient strength to maintain a regular rate, at which time the auto-timer is closed and the dog's respirations are again assisted until he has an adequate exchange of his own.

TABLE I. ARTERIAL O_2, CO_2, AND pH ANALYSES IN THE ANESTHETIZED DOG 15 MINUTES AFTER THE CHEST IS OPENED AND 30 MINUTES POSTOPERATIVELY

	15 MIN. POST INDUCTION			15 MIN. POST THORACOTOMY			30 MIN. POSTOPERATIVE		
DOG NO.	O_2%	CO_2%	pH	O_2%	CO_2%	pH	O_2%	CO_2%	pH
18	97		7.35	99		7.38	96.5		7.30
21	96		7.35	97		7.30	97		7.40
24	100		7.6	100		7.56	100		7.5
25	99.5	33	7.65	99	28	7.7	99	26	7.5
27	98.5	34	7.6	99	32	7.7	98	30	7.6
29	96	32	7.4	99	28	7.6	96.5	26	7.4
31	97	37	7.4	98	32	7.4	96	28	7.3
32	98	31	7.6	98	26	7.4	95	26	7.4

As noted in Table I, the arterial oxygen, carbon dioxide, and pH studies on 8 dogs that underwent open-heart operations, in which the mitral valve was replaced with a prosthesis, are well above the expected values for this type of surgery. These are attributed to the technique just described which assists rather than opposes pulmonary ventilation.

SUMMARY

A simple method of administering assisted-controlled anesthesia to dogs, which utilizes a minimum of compact equipment, is described.

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HEMOLYSIS IN DOG BLOOD: IN VITRO EXPERIMENTS

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IN A SERIES of experiments on dogs, it has been demonstrated that hyperventilation resulting in alkalosis produced a marked increase in free hemoglobin concentration in plasma in the majority of the experiments. Most of the available knowledge concerning the breakdown of erythrocytes seems to originate from the study of anemias. Interest has been focused on factors involved in the normal destruction of red blood cells and in the conditions responsible for the occurrence of a hemolytic episode. In a monograph and numerous articles, Ponder[13] has discussed at length the various aspects of all these problems. According to these publications the old "wear and tear" theory of erythrocyte destruction appears to have lost ground. A better understanding of the manifold aspects of the problem is gained if the breakdown of a red blood cell is considered the end result of a continuous aging process, metabolic in nature and involving a using-up of enzymes and perhaps other material essential to the cell's integrity. The final disintegration of the cell may be the result of agglutinin-lysin complexes, influence of chemical substances, or mechanical damage. It is pointed out that the red cell contains all the essentials of a lysin-inhibitor system within its own structure. The occurrence of a hemolytic episode is dependent on several of these factors. The concentration of plasma lysins and agglutinins is of importance and so is the balance between inhibitors and accelerators. Temperature, pH, and certain electrolytes exert an additional influence on the action of these systems.[13]

It has been demonstrated that mechanical fragility may be increased in diseases characterized by hemolysis (Shen, Castle, and Fleming[14]). These authors have designed a method for quantitative measurement of the mechanical fragility. By means of this, increased mechanical fragility was demonstrated in congenital hemolytic jaundice and after thermal burns. Furthermore, a relationship was found to exist between osmotic and mechanical fragility. A discrepancy has been demonstrated, however, in the case of pernicious anemia and in certain experimental conditions (Dameshek and Miller[5]).

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During hyperventilation with lowering of pCO_2 and decrease in hydrogen ion concentration, the stability of the systems of the erythrocytes must be attacked from several angles. Studies indicated that this was without influence on the osmotic fragility of the erythrocytes.[2] This publication deals with the investigation of the influence on mechanical fragility.

TECHNIQUE AND METHODS

A technique was designed and used for quantitative studies of the factors involved in the hemolysis due to hyperventilation. The method must allow for exposure of the blood sample to a certain mechanical trauma, as well as known variations in pCO_2 and pO_2. Variations in concentration of free hemoglobin in the plasma will reflect the degree of breakdown of red blood cells.

A coefficient of mechanical fragility may be expressed as produced hemolysis measured by the concentration of liberated hemoglobin divided by the total amount of hemoglobin that can be delivered from the erythrocytes by complete hemolysis of the sample. As the interest from the point of view of the present investigation is a term expressing the resistance of the erythrocytes, the term "mechanical resistance" (MR) is used. This may be defined as the percentage of erythrocyte-bound hemoglobin remaining cell-bound after exposure.

It is determined as follows:

$$MR = \frac{\text{total hemoglobin of blood sample} \div \text{experimentally produced hemoglobin in plasma}}{\text{total hemoglobin of blood sample}} \times 100.$$

Blood for the studies was obtained from mongrel dogs bled usually by percutaneous puncture of the femoral artery under a light Nembutal anesthesia (30 mg. per kilogram). Siliconized, cylindrical test tubes with a flat bottom (3.65 cm. by 10.15 cm.) were used. Twelve milliliters of blood was introduced into the tubes which were placed on the rollers of a mechanical apparatus designed for continuous rolling of such tubes. A speed of 127 r.p.m. was used. The tubes were kept in an oblique position at 10 degrees to the horizontal plane. By this arrangement, the blood was spread on the inside of the glass producing a thin film. This film of blood was exposed to a current (1.5 liters per minute) consisting of either pure oxygen or Carbogen (a mixture of 96 per cent oxygen and 4 per cent carbon dioxide). The gas passed through a water bath and was blown through a thin glass pipe placed in the axis of the revolving cylindrical tube. At the same time, a blood specimen in a third tube was exposed to static room air, as this tube during the rotation was closed with nonabsorbent cotton. All experiments have been carried out at a temperature of 37° C.

Three of the heparin-blood samples were drawn from dogs made acidotic by ingestion of ammonium chloride (NH_4Cl). For these experiments, freshly drawn blood was used as well as blood stored for various periods of time at 2° to 4° C. in sterile, siliconized bottles.

The following determinations were carried out: pH, plasma hemoglobin, and hematocrit before and after 10, 20, and 30 minutes of rotation. In most instances, also, the total hemoglobin content of the blood sample was determined.

The pH determinations were done on whole blood at 38° C. with the apparatus designed by Astrup.[1] The plasma hemoglobin determinations were

carried out according to the method described by Zijlstra.[15] Hematocrit was measured in Wintrobe tubes after centrifugation for 10 minutes at 6,000 r.p.m.

RESULTS

The results obtained have been tabulated in Table I. Fig. 1 illustrates the alterations produced in pH and pCO_2 values when a sample is exposed to (a) pure oxygen, and (b) Carbogen.

When blood was sampled with heparin (1 mg. per 10 milliliters of blood) the starting pH values were within the range of 7.25 to 7.48. In samples exposed to atmospheric air and oxygen, the pH values increased to between 8 and 8.25 in the 20- and 30-minute samples. In the blood exposed to Carbogen, the values levelled off, reaching values between 7.24 and 7.45. The values of free hemoglobin concentration in plasma reached different values whether it was a blood sample exposed to air, to oxygen, or to Carbogen (Fig. 2). When *oxygen* was used, a marked elevation occurred in the 10-minute sample. The greatest

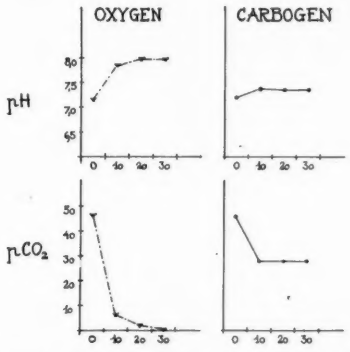

Fig. 1.—A graphic presentation of the pCO_2 and the pH changes in the blood samples with the technique described. Values are given before (zero values) and after 10, 20, and 30 minutes of exposure to pure oxygen or Carbogen (trade name for 96 per cent oxygen and 4 per cent carbon dioxide). Greatest change takes place within 10 minutes.

increase appeared between 10 and 20 minutes, although the 30-minute sample also showed the increase to have continued. When *atmospheric air* was used, the increase was similar to the one produced by oxygen. The total increase was usually somewhat smaller than that produced by pure oxygen. When the *Carbogen* was applied, the plasma hemoglobin usually showed only a slight increase.

The *hematocrit values* tended to decrease, related to the increase in free hemoglobin. However, no proportional relationship seems to exist between the degree of hemolysis and the fall in hematocrit. This applies to the samples exposed to oxygen and atmospheric air; in the samples exposed to Carbogen, slightly increasing hematocrit values were found. In blood sampled in ACD solution, exposure to oxygen produced a slight decrease in hematocrit, while the corresponding hematocrit change produced by Carbogen is an increase. These findings from samples without hemolysis may indicate the general trend of the hematocrit values preceding the episode of hemolysis.

Blood from 10 of the 14 dogs tested in this way reacted as just outlined. Blood from the remaining 4 dogs behaved differently. In blood from these 4 dogs (58-088, 58-122, 59-025, and 60-012) only slight hemolysis was produced by exposure to oxygen.

Applying the MR coefficient, defined above, to the findings with blood in heparin, it is found that exposure to Carbogen through 30 minutes gives figures varying from 100 to 94. When atmospheric air has been applied, the figures for MR vary from 99 to 22. Exposure to oxygen results in figures extending from 98 to almost 0. (Survey based on mean values is given in Fig. 3, *A*.)

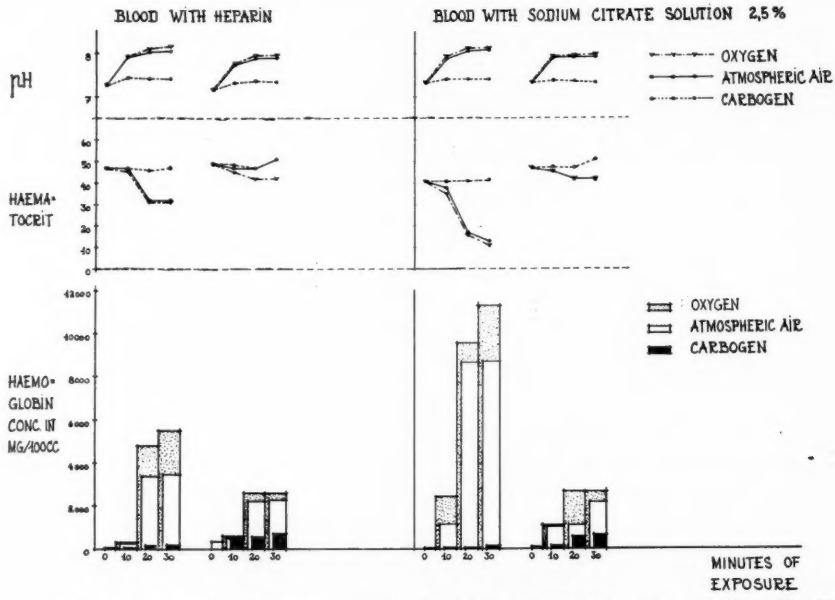

Fig. 2.—A graphic presentation of free hemoglobin concentration, hematocrit, and pH changes after exposure to oxygen, atmospheric air, and Carbogen in 10, 20, and 30 minutes. The figure illustrates the findings when heparinized blood was used (first column represents findings in fresh blood, second those after 24 hours' storage at 4° C.). Similarly the findings from blood preserved with neutral sodium citrate solution.

The MR figures are plotted against the pH values obtained at the end of 10, 20, and 30 minutes of exposure to oxygen in Fig. 4. This indicates that mechanical resistance is reduced when pH is above 8.0. Fig. 5 illustrates the changes of MR values obtained by exposure to Carbogen and to oxygen plotted against the corresponding pH values.

This leaves one with the idea that exposure to oxygen resulting in elimination of CO_2 and elevation of pH above 8 lowers the mechanical resistance of the red blood cells. In 2 dogs (58-088 and 58-122), evidence exists that acidosis had been present. Similar alterations were not found in dogs 59-025 and 60-022. Blood samples were studied in order to elucidate the influence of storage, the influence of anticoagulants applied, etc.

Blood from 3 dogs was collected in a neutral 2.5 per cent sodium citrate solution (1 ml. per 10 milliliters of blood) and submitted to the same experimental procedure as outlined above. pH at the start of the procedure was from 7.32 to 7.48. By exposure to pure oxygen, the pH values reached approximately 8 in the 10-minute sample and above 8 in all 3 of the 20-minute and 30-minute samples. The concentration of free hemoglobin in plasma rose by exposure to oxygen and atmospheric air to very high values in 2 of the dogs, while

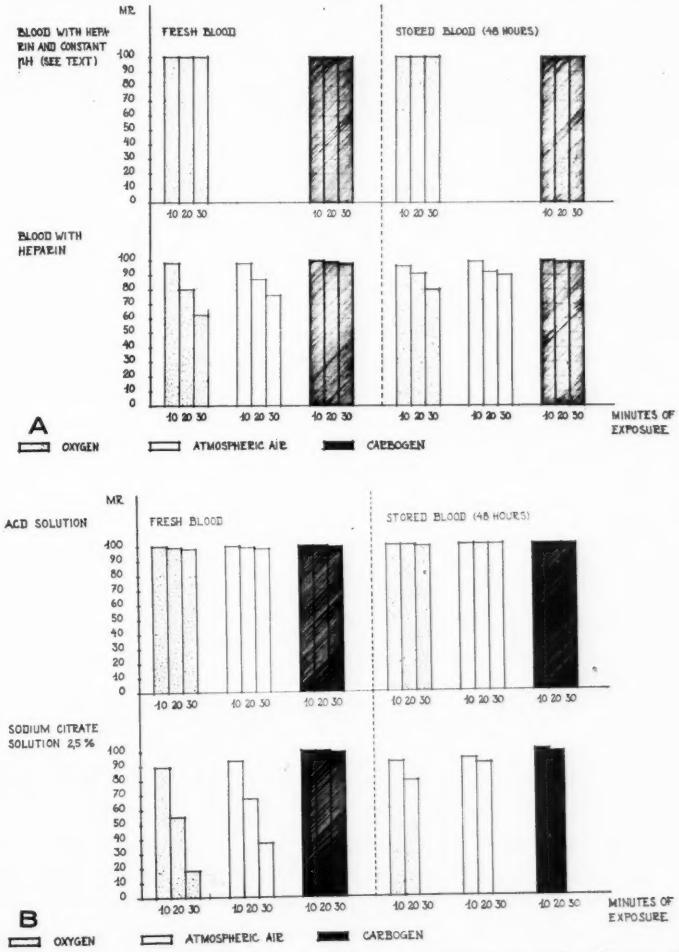

Fig. 3.—A graphic presentation of mean values for MR (mechanical resistance of erythrocytes, for definition see text) obtained following exposure to pure oxygen, atmospheric air, or Carbogen in 10, 20, and 30 minutes.

A gives the findings when fresh and stored heparinized blood was used. Also illustrated are the findings in blood from animals fed with ammonium chloride 2 hours prior to blood sampling in order to obtain blood with a pH stabilized as a result of a metabolic acidosis.

B gives the findings from blood preserved with neutral sodium citrate solution and ordinary ACD solution.

in the third (58-186), the maximum value reached was 483 mg. per cent in the 20-minute sample (a 30-minute sample was not obtained in this case). After exposure to Carbogen, the pH values remained almost unchanged in all 3 cases, the lowest value being 7.33. Here in all 3 dogs, the free hemoglobin remained below 150 mg. per cent.

As a result of the examination of the blood of 3 dogs collected in a 2.5 per cent citrate solution it may be stated that the pattern of hemolysis is quite similar to that observed with blood samples collected in heparin, the only deviation being the more pronounced hemolysis in the citrate solution (see Fig. 2).

Similarly, experiments were carried out with blood collected in ACD solution "A" USP XV (65 ml. per 500 ml. of blood). Blood from 7 dogs was tested (Table I).

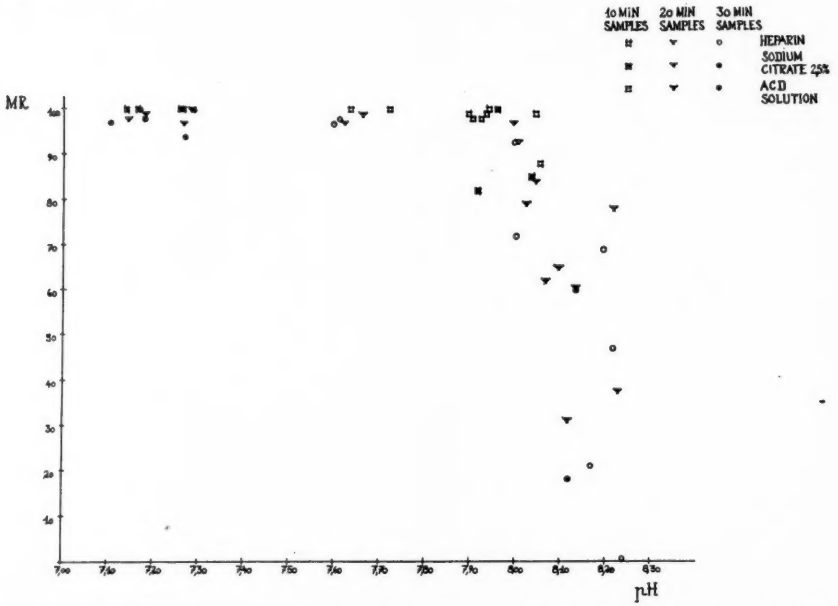

Fig. 4.—MR (mechanical resistance) figures plotted against the pH values obtained. Definite reduction in mechanical resistance of red blood cells occurs when pH reaches values above 8.

As is to be expected, the starting pH values in these blood samples are all below 7, the lowest being 6.03 and the highest 6.81. Exposure to oxygen, atmospheric air, and Carbogen results in an increase in pH in all cases. The oxygen exposure carries a pH to levels between 7.2 and 7.3, while atmospheric air leads to pH values around 7.2. When it comes to the exposure to Carbogen the pH values in only one sample rise above 7. The maximum value was 7.01, being reached in blood from dog 59-013. The resulting figures of free hemoglobin in plasma showed both with low values of oxygen, atmospheric air, and Carbogen. The MR values were 94 and 100 with oxygen, between 99 and 97 with atmospheric air, and between 97 and 100 with Carbogen.

In order to study the effect of a pH stabilized by means unrelated to the carbon dioxide, blood from animals given ammonium chloride prior to blood sampling was studied.

Ammonium chloride (0.3 Gm. per kilogram of body weight) was given to 3 dogs 2 hours before blood sampling. Heparin was used as the anticoagulant. The pH values are low, between 7.05 and 7.20, and, as is apparent, the increase accomplished by the exposure to oxygen is much less than it is in blood from the same animals, when no premedication with NH_4Cl was given. The concentration of free hemoglobin in plasma remains low. The blood samples behave like the ones with blood drawn directly into citrate-citric acid-dextrose buffer solution (Fig. 3, *B*).

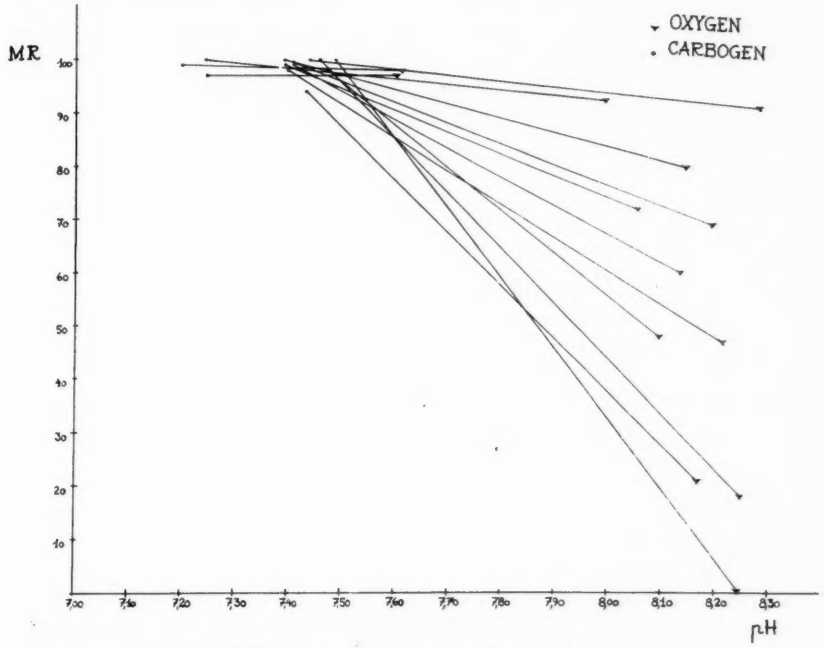

Fig. 5.—Corresponding mechanical resistance values obtained by 30 minutes' exposure to Carbogen and to oxygen are plotted against the pH values obtained in the samples. The greater the shift in pH, the greater the reduction in the mechanical resistance of the erythrocytes.

The blood samples from the various animals were also examined after storage. This included various types of anticoagulants used. No alterations in the MR were found to take place by exposure to oxygen, when citrate-citric acid-dextrose buffer solution was used. When the blood had been drawn into heparin or an ordinary 2.5 per cent sodium citrate solution, an increase in MR values was noted within the first 24 hours (Fig. 3, *B*). A few pilot experiments testing blood samples stored in heparin and citrate indicate that the tendency for the production of hemolysis by exposure to oxygen and room air is reduced by storage.

TABLE I

DOG NO.	pH	HEMATOCRIT	TOTAL HEMOGLOBIN (MG. %)	100% O_2 IN 30 MINUTES				ATMOSPHERIC AIR IN 30 MINUTES				4% CO_2 + O_2 IN 30 MINUTES			
				pH	INCREASE IN PLASMA HEMOGLOBIN (MG. %)	MR	HEMATOCRIT	pH	INCREASE IN PLASMA HEMOGLOBIN (MG. %)	MR	HEMATOCRIT	pH	INCREASE IN PLASMA HEMOGLOBIN (MG. %)	MR	HEMATOCRIT
Fresh, Heparinized Blood															
58-011	7.371	42	12,780	8.24	12,755	< 1	23	—	—	—	—	7.489	36	100	41
58-043	7.248	44	11,800	8.22	6,273	47	21	—	—	—	—	7.400	228	98	44
58-138	7.284	40	13,760	8.14	5,472	60	31	8.06	3,395	75	32	7.409	142	99	47
58-157	7.338	37	11,260	8.20	3,529	69	21	—	—	—	—	7.408	148	99	33
58-175*	7.422	37	—	8.21	2,909	—	25	—	—	—	—	7.508	18	—	37
58-185	7.271	43	11,440	8.06	3,257	72	38	8.05	1,417	88	39	7.395	160	99	44
59-013	7.400	42	12,740	8.17	10,065	21	10	8.12	9,852	22	16	7.431	821	94	45
59-025	7.401	45	11,720	8.02	857	93	41	—	—	—	—	7.245	54	100	48
58-088	7.146	37	9,804	7.613	178	98	37	7.601	141	99	37	7.200	120	99	43
58-122	7.209	67	14,890	7.601	510	97	66	7.600	493	97	70	7.249	378	97	69
57-053	7.420	49	14,160	8.10	7,390	48	35	—	—	—	—	7.475	276	98	50
60-023	7.478	26	7,860	8.15	1,510	80	21	—	—	—	—	7.395	11	100	27
60-022	7.418	32	9,115	8.29	665	91	29	—	—	—	—	7.441	3	100	32
60-016	7.355	45	13,430	8.25	11,011	18	8	—	—	—	—	7.460	65	100	45
Blood From Dogs Given NH_4Cl Prior to Experiment															
58-043	7.075	45	11,800	7.675	65	100	42	—	—	—	—	7.241	58	100	48
58-157	7.198	42	11,260	7.711	51	100	40	—	—	—	—	7.288	36	100	41
59-038	7.140	54	14,890	7.470	61	100	55	—	—	—	—	7.208	43	100	56
Blood With 2.5% Sodium Citrate Solution as Anticoagulant															
58-138	7.325	41	13,760	8.12	11,250	18	11	8.11	8,639	37	13	7.409	149	99	42
58-186*	7.321	51	14,340	8.00	483	97	51	7.970	199	99	51	7.325	65	100	51
58-225*	7.488	32	9,804	8.23	6,100	38	22	8.10	3,377	65	23	7.359	51	99	33
Blood With ACD Solution as Anticoagulant															
57-161	6.805	44	11,290	7.290	25	100	42	—	—	—	—	6.882	21	100	45
58-088	6.810	35	9,077	7.107	164	97	33	—	—	—	—	6.923	145	98	36
58-122	6.761	51	12,710	7.181	232	98	48	7.204	145	99	54	6.987	120	99	56
58-166†	6.672	26	—	7.225	4	—	24	7.220	4	—	24	6.810	4	—	25
58-185‡	6.035	34	9,114	6.309	90	99	32	6.282	90	99	32	6.240	68	99	33
59-013	6.762	42	11,260	7.271	664	94	38	7.265	327	97	37	7.012	302	97	41
59-025	6.766	45	11,550	7.165	54	100	44	—	—	—	—	6.867	29	100	50

*Only 20 minutes' rolling.
†45 minutes' rolling.
‡200 ml. blood taken with 65 ml. ACD solution.

DISCUSSION

As mentioned in the introductory remarks, the integrity of the red blood cell rests normally on a complicated interplay of factors acting primarily within the red blood cell itself and factors located in the surrounding plasma. As pointed out by Dameshek,[6] the exact mechanisms involved in normal red blood cell destruction are quite obscure. Attempts to incriminate a single mechanism as solely responsible for all hemolytic states are probably unwarranted.

The results of the investigations reported indicate that red blood cells are less resistant to a certain mechanical trauma when exposed to high oxygen concentrations and lowering of the pCO_2 leading to an increase in pH.

The occurrence of hemolysis in blood samples exposed to high oxygen tensions is an old laboratory experience (Haggard and Henderson,[9] Jørgensen and Astrup,[10] Møller,[11] and Plum[12]). According to publications dealing with hemolysis occurring during the passage of blood through oxygenators, similar observations have been made (Gott and associates,[8] Bücherl,[4] Ferbers and Kirklin[7]). This background adds practical interest to the matter of this type of hemolysis.

The hydrogen ion concentration seems to be of particular importance. The mechanical fragility index used indicates that red blood cells can resist the mechanical trauma applied with the technique described when pH is kept below 8.0. It seems without importance whether this is accomplished by keeping the pCO_2 above a certain level or by buffering the plasma by ACD solution or NH_4Cl. On the other hand, the few exceptions from the general pattern point to other factors in addition to pH as influencing the red cell's resistance toward mechanical forces. The results of our investigations do not allow for any conclusions as to the mechanism of the hemolysis observed in our experiments. One can only speculate as to the factors involved.

During the early part of the investigations, the observed hemolysis was thought to be the result of quick oxidation. Support for this idea could be found in the interplay of the enzyme catalase and the formation of choleglobin through methemoglobin (Ponder[13]). However, the same hemolysis may be produced by exposure to pure nitrogen. Later it was attempted to correlate the hemolysis with the water-electrolyte shifts during the respiratory activity of the red blood cell. To approach the validity of this explanation, an attempt was made to correlate the mean cell hemoglobin concentration with the degree of hemolysis. No significant relationship was found, however.

The observations reported seem to be of interest from the point of view of the pump oxygenator technique. In the work of Ferbers and Kirklin,[7] control values were obtained with atmospheric air in the oxygenator. According to our findings this is not justified as the pH of the circulating blood may increase equally by exposure to oxygen and atmospheric air. In consequence of our findings, studies are in progress using pump oxygenator aggregates of various types.[3] The hemolysis obtained by exposure to a certain oxygen-carbon dioxide mixture serves as the control value, while the values obtained by exposure to pure oxygen or atmospheric air serve as indicators of the damage produced by

the machinery. The observations made so far seem to indicate that hemolysis produced in pump oxygenators is not the simple result of mere mechanical damage, rather it seems to be related to the gas exchange capacity of the oxygenator.

SUMMARY AND CONCLUSIONS

In hyperventilation studies on dogs it was observed that intervascular hemolysis was produced. In vitro studies on dog blood were carried out. The data obtained are reported. The results indicate that lowering of the hydrogen ion concentration in blood leads to a reduction of the mechanical resistance of the red blood cells. In view of this, a re-evaluation of earlier investigations concerned with the occurrence of hemolysis during pump-oxygenator experiments is indicated.

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EMERGENCY CORONARY ENDARTERECTOMY

Case Report

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CORONARY ENDARTERECTOMY has been performed electively in the treatment of incapacitating angina pectoris by several surgeons.[1, 2, 3] To our knowledge, however, no one has attempted an emergency coronary endarterectomy to restore cardiac function when routine resuscitative measures had failed after acute coronary occlusion.

We are reporting in detail the clinical course of a 52-year-old man who suffered cardiac standstill after an acute coronary occlusion. Normal rhythm and function could not be restored with intermittent cardiac compression alone, but were restored after coronary endarterectomy and re-establishment of blood flow to the compromised heart muscle. The patient died after 52 hours following sudden anoxia and ventricular fibrillation.

CASE REPORT

On Feb. 25, 1960, a 52-year-old white truck driver came to our office (J. F. B.) at the Massachusetts General Hospital because of abdominal pain of about 2 months' duration. Shortly after arriving in the waiting room the patient arose to get a drink of water and while crossing the hall to the fountain fell to the floor in convulsions. He was seen immediately, a diagnosis of cardiac arrest made, the left chest opened, and intermittent cardiac compression begun. He was oxygenated initially by mouth-to-mouth insufflation, spontaneous respirations resumed after about 1 minute of cardiac compression, and an endotracheal tube was passed in order to give more adequate oxygenation and anesthesia.

The past history was obtained from the patient and the patient's wife after the surgical procedure. They indicated that for the 2 months prior to his admission he had suffered epigastric distress, associated with belching, which was relieved by antacids. The pain occurred mostly at night and was not associated with exercise. There was no history of edema, dyspnea, or radiation of the pain.

Upon opening the chest, the heart was found dilated and in asystole (Fig. 1). After about 3 minutes of massage there was a faint flicker of activity from the right ventricle but no effective beat. The patient was immediately taken to the operating room and the initial incision extended transsternally. Massage was continued and after about 10 minutes the

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auricles and right ventricle began to contract but there was no resumption of activity in the left ventricle. At this time the patient's systolic blood pressure could be maintained at 60 to 80 mm. Hg as measured by a blood pressure cuff by allowing the right ventricle to perfuse the pulmonary bed while the systemic bed was being perfused, using manual systole restricted to the left ventricle. Inspection of the right coronary and the left descending coronary vessels could be carried out while the left ventricle was being intermittently compressed. This showed a 1 cm. area of thick scarring about the left descending vessel just below the take-off of the circumflex branch. At this site the artery appeared and was felt

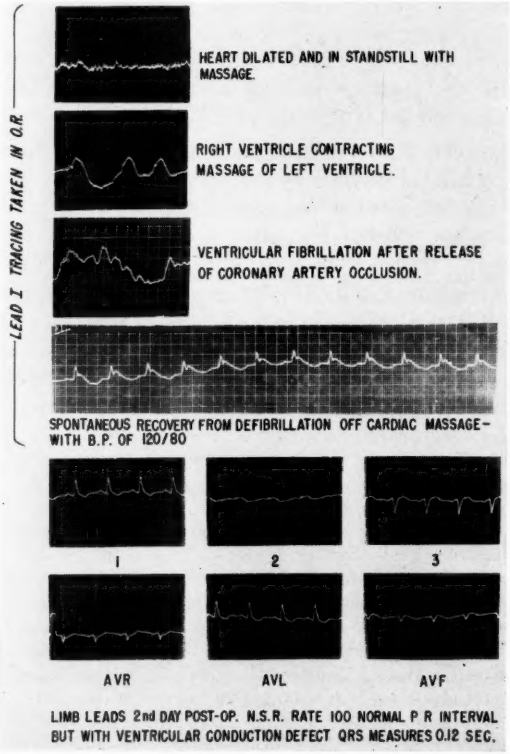
LEAD I TRACING TAKEN IN O.R.
HEART DILATED AND IN STANDSTILL WITH MASSAGE.
RIGHT VENTRICLE CONTRACTING MASSAGE OF LEFT VENTRICLE.
VENTRICULAR FIBRILLATION AFTER RELEASE OF CORONARY ARTERY OCCLUSION.
SPONTANEOUS RECOVERY FROM DEFIBRILLATION OFF CARDIAC MASSAGE-WITH B.P. OF 120/80
1
2
3
AVR
AVL
AVF
LIMB LEADS 2nd DAY POST-OP. N.S.R. RATE 100 NORMAL P R INTERVAL BUT WITH VENTRICULAR CONDUCTION DEFECT QRS MEASURES 0.12 SEC.

Fig. 1.—Electrocardiograph tracings made before, during, and after coronary endarterectomy.

to be occluded over a distance of about 1.5 cm. The circumflex branch and the posterior descending coronary looked and felt relatively free of disease. Because it was possible to maintain circulation by manual systole of the left ventricle alone without compromising the exposure of the occluded area in the anterior descending artery, and because of our desire to be expeditious, no attempt was made to maintain the patient by extracorporeal circulation or hypothermia. Approximately 20 minutes after the arrest, because an effective heartbeat could not be established, the anterior descending coronary artery was isolated above and below the scarred area, immobilized with loops of No. 2 Deknatel suture material, and opened with a 1 cm. longitudinal incision (Fig. 2). A well-organized thick yellow tube of atheroma was found and divided. The proximal portion was freed and removed which resulted in a good pulsatile flow of bright red blood. The proximal loop of Deknatel was tightened after the

proximal artery was filled with a dilute heparin solution. A 1.5 cm. tube of atheroma was removed from the distal segment (Fig. 3). This contained a fresh thrombus which extended down to within 5 mm. of the distal end where the atheroma branched into two tributaries of about equal size. The fresh thrombus did not extend into either of these branches. Upon removal of this branched atheroma, there was sluggish back bleeding of dark blood. The distal tree was then filled with a dilute heparin solution and the arterotomy closed with 6-0 arterial silk. No systemic anticoagulants were administered. All through this period of endarterectomy the systolic blood pressure was maintained at a level of 60 to 80 mm. Hg by manual systole.

Fig. 2.—Photograph which shows manual systole of the left ventricle while coronary endarterectomy is being done.

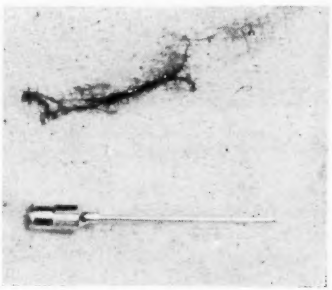

Fig. 3.—Surgical specimen which shows branch atheroma and fresh clot.

After closure of the arterotomy and re-establishment of flow, the left ventricle fibrillated (see Fig. 1). This did not affect the normal beat of the right ventricle and within a minute the left ventricle reverted to a sinus rhythm. The patient's systolic blood pressure was then recorded at 80 mm. Hg and the chest was closed. During the closure the ECG steadily improved (see Fig. 1) and by the end of the operation the blood pressure was spontaneously maintained at 120/80 mm. Hg. The patient had spontaneous respirations and responded to pain.

He was taken to the recovery room where his state of consciousness steadily improved. Urine output was well maintained at all times. He continued to make good progress until

the evening of the first postoperative day, when the breath sounds at the bases of both lungs became diminished and he became hypotensive. He was given a whole blood transfusion during the night which stabilized his blood pressure. This was the only blood given the patient. Tracheal suctioning did not improve the breath sounds at the bases of the lungs. A portable chest roentgenogram at this time showed clear noncongested upper lobes. On the second postoperative day it was necessary to give Levophed to maintain blood pressure. The pulmonary congestion increased and ventilation became increasingly difficult. In spite of progressive difficulty with ventilation, the urine output continued at 50 c.c. per hour and his mental state continued to improve. Fifty-two hours after endarterectomy, he vomited, became anoxic, had a sudden bout of ventricular fibrillation, and died.

Fig. 4.—Injected autopsy specimen showing endarterectomy site open. *Arrow* indicates point 1 cm. below the site of endarterectomy where vessel was re-occluded by atheroma and fresh thrombus.

Autopsy revealed a hypertensive heart, weighing 480 grams, with severe coronary disease. The lumen of the endarterectomized vessel was patent and the suture line was intact without significant narrowing. Approximately 1 cm. beyond the operative site, the vessel was occluded by atheroma and fresh thrombus (Fig. 4). At this site there was a recent myocardial infarct involving the lower anterior left ventricle. There was bilateral bronchopneumonia and slight pulmonary congestion and edema.

DISCUSSION

The surgery of coronary insufficiency is still in an early developmental phase. It is impossible at present to evaluate what benefits may be expected from coronary endarterectomy, either on an elective or emergency basis. We are aware that some patients with acute ventricular fibrillation and standstill have been resuscitated with survival by conservative measures.[4, 5] Such success

has been rare and the myocardium is permanently taxed by the loss of function secondary to a myocardial infarction. Nevertheless, if an effective heartbeat can be reinstituted by massage and other conservative measures, we believe endarterectomy cannot yet be justified as an emergency measure. Our decision to proceed with endarterectomy could not be long delayed since there is evidence[6] that little is to be accomplished after a delay of an hour or longer. It is likely that this type of procedure should be facilitated by the appropriate use of hypothermia and cardiac bypass. In this particular case it was thought that the delay involved in instituting these measures would be more deleterious than beneficial.

It would seem that the acute obstruction resulted from a thrombus forming in an area of atheromatous narrowing. Death presumably resulted from pulmonary insufficiency as well as residual occlusion in a more distal site of the coronary tree. It seems likely that if this patient had had less diffuse disease our efforts might have been more successful. From a technical point of view, it is highly significant that an endarterectomized coronary artery remained patent and without significant narrowing for a period of 52 hours without use of systemic anticoagulants.

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ACCESSORY BICUSPID AORTIC VALVE: A VARIANT OF SUBVALVULAR AORTIC STENOSIS

Case Report

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IN 1927, Enzer[10] reported a variant of subvalvular aortic stenosis. He described a case in which a fibrous shelf appeared in the form of two leaflets to which chordae tendineae were attached and which resembled two miniature mitral leaflets. Recently we encountered a similar case. Its apparent rarity and unusual mechanism of obstruction prompted us to report it.

CASE REPORT

The patient was a 19-year-old girl who had immigrated from Greece 18 months previously. She was admitted to the Allegheny General Hospital on March 17, 1960, having been referred for diagnostic studies and treatment. Until 5 years previously, she had been well and tolerated normal physical activity. Since then she had experienced progressive dyspnea on exertion, recurrent palpitations, and a precordial ache. Prior to admission, symptoms would develop if she walked more than one street block or up one flight of stairs. There was no history of cyanosis, edema, orthopnea, cough, or hemoptysis. Personal and family history were noncontributory. There was no history suggesting rheumatic fever during childhood.

Physical examination revealed a short but well-developed and well-nourished white girl with good color and no cyanosis. Positive findings were limited to the cardiovascular system. The chest was well formed and the lungs clear to percussion and auscultation. The point of maximal impulse was in the mid-clavicular line in the fifth intercostal space. A systolic thrill was faintly palpable at the suprasternal notch. The heart rate was regular at 74 per minute. A loud Grade 4 systolic murmur was audible at both the upper left and right sternal borders. P_2, A_2 and M_1 were of normal intensity. The blood pressure was 110/80 mm. Hg. The peripheral veins were not distended and there was no edema. Peripheral pulses were normal bilaterally.

Laboratory Data.—Hemogram, blood chemistry, antistreptolysin-O titer, sedimentation rate, and urinalysis were within normal limits. Fluoroscopic examination of the chest revealed slight prominence of hilar pulmonary markings. No valve calcification was evident. X-rays of the chest with barium swallow suggested left ventricular enlargement (Fig. 1). The electrocardiogram showed nonspecific T wave changes and slight widening of the QRS complex. No right or left heart preponderance was evident (Fig. 2).

The initial diagnostic impression was of either congenital pulmonic or aortic stenosis. Standard right heart catheterization was performed on March 17, 1960, revealing elevated right ventricular, pulmonary artery, and pulmonary capillary pressures, but no evidence of a left-to-right shunt. A combined left and right heart catheterization was subsequently

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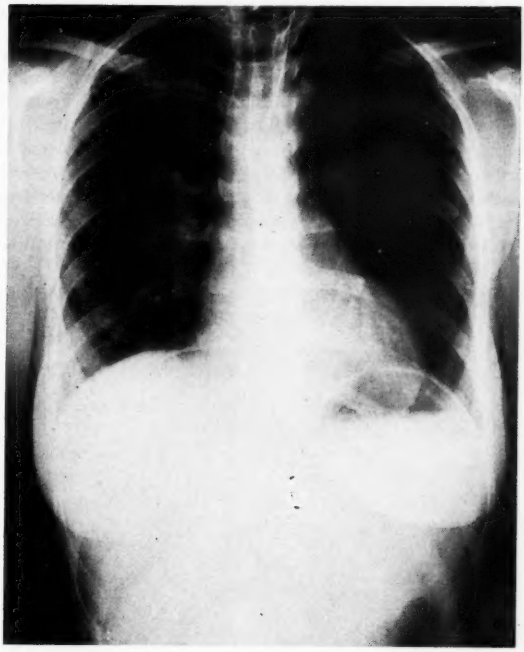

Fig. 1.—Film of the chest with barium swallow suggests left ventricular enlargement.

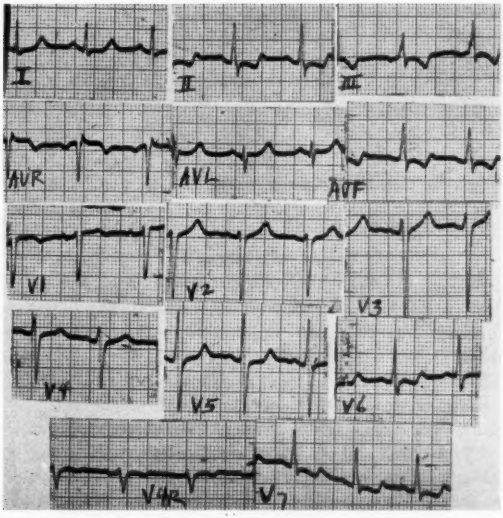

Fig. 2.—Electrocardiogram which shows nonspecific T wave changes and slight widening of the QRS complex.

performed on March 18, 1960. Careful pressure tracings taken as the catheter passed from the left ventricle into the aorta, then back again, were typical of aortic valvular stenosis with a systolic gradient of 80 mm. Hg (Fig. 3). No subvalvular chamber was detected and the transition appeared sharp. The effective calculated aortic valve orifice was 0.9 cm.^{2} (0.6 /M.^{2}).[12] The cardiac index was normal (3.3 L./min.). There was no mitral stenosis.

On March 25, 1960, the patient was taken to the operating room and the heart was exposed through a right thoracotomy incision. The ascending and proximal aorta appeared normal. A prominent rough systolic thrill was palpable over the aortic root. The pulmonary artery was not remarkable and the heart did not appear enlarged. Following insertion of the vena caval catheters via the right atrium and an arterial catheter into the right femoral artery, the patient was connected to a pump-oxygenator and put on partial circulatory bypass.

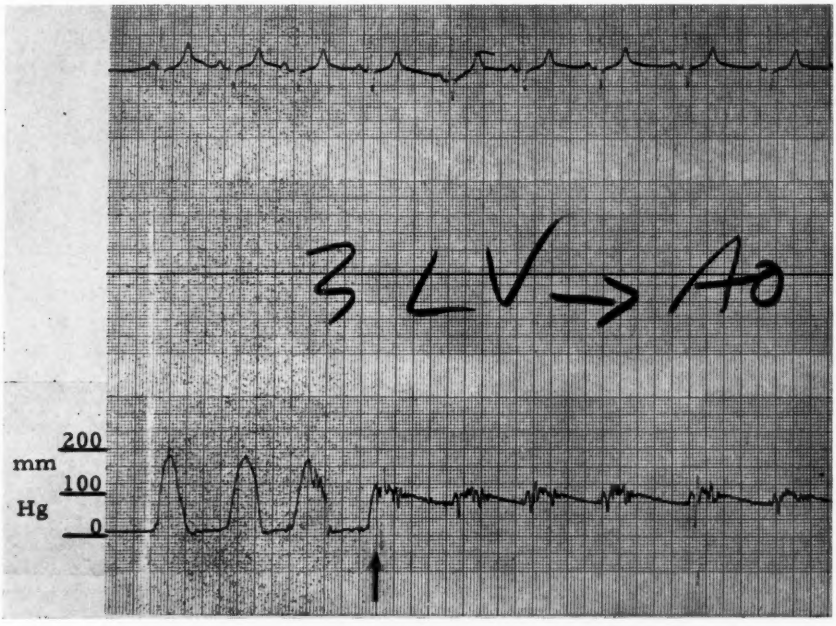

Fig. 3.—Pressure tracing as the catheter passed from the left ventricle to aorta. Note the sharp transition *(arrow)* with a systolic pressure gradient of 80 mm. Hg and no indication of a subvalvular chamber.

A heat exchanger in the circuit cooled the blood and the patient's temperature was lowered to 31.5° C. Complete bypass was then instituted, the ascending aorta cross-clamped, and a 5 cm. longitudinal incision made into the right posterolateral aspect of the aortic root, extending to 1 cm. above the valve cusps. The edges of the aortotomy were retracted, exposing a thickened bicuspid valve. In spite of partial fusion of the commissures, the valve orifice appeared adequate and permitted insertion of the index finger into the left ventricle. No subvalvular obstruction, either muscular or fibrous, was encountered. Chordae tendineae were felt just under the subvalvular area, but these were interpreted as being related to the aortic leaflet of the mitral valve. Since the aortic valve seemed adequate, no attempt was made to divide the fused commissures. Throughout the exploration, the left ventricle continued to eject blood, even though the caval catheters seemed properly occluded, and the heart continued to beat regularly. A Satinsky clamp was applied to the aortotomy and the clamp across the ascending aorta removed. As the aortotomy incision was closed, the patient was kept

on partial circulatory bypass, which was gradually discontinued. The duration of total bypass was 16 minutes. The patient was disconnected from the pump-oxygenator, venous and arterial catheters were removed, a lower drainage tube was inserted, and the chest was closed.

The immediate postoperative course was not remarkable. During the next 48 hours there was drainage of 3,000 c.c. of bloody fluid from the right chest and the patient required transfusion with 7 units of blood. Chest x-rays revealed opacification at the right base, probably representing a hemothorax. The patient, however, was comfortable and appeared to be doing well. On the evening of the second postoperative day she became restless and uncooperative. Shortly thereafter she suddenly developed respiratory and cardiac arrest. Left thoracotomy was carried out and cardiac massage instituted within 6 minutes. Although the heart was successfully resuscitated, the patient never regained consciousness. After the left chest was closed, 1,000 c.c. of blood clot was evacuated from the right pleural cavity by reopening the original incision. Spontaneous respirations never returned and vasopressors were required. The patient was connected via an endotracheal tube (and later a tracheostomy tube) to a respirator and the body temperature maintained at 32° C. Her condition gradually deteriorated and she died the following day.

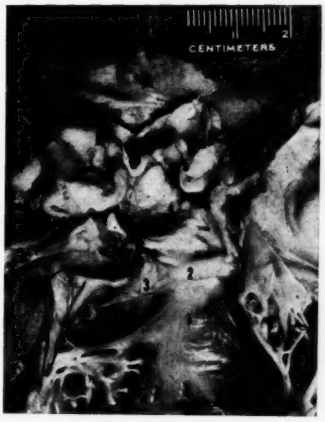

Fig. 4.

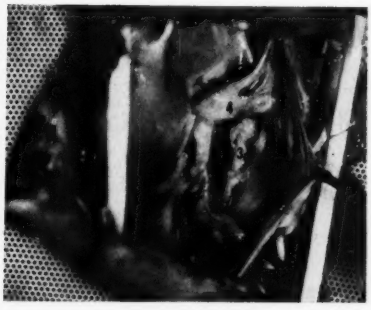

Fig. 5.

Fig. 4.—Photograph of the outflow tract of the left ventricle illustrating: *1*, the muscular septum; *2*, the fibrous subvalvular shelf; *3*, the miniature mitral-like leaflets; *4*, the subvalvular chamber; *5*, the aortic valve.

Fig. 5.—Photograph of outflow tract of left ventricle from below illustrating: *1*, the muscular septum; *2*, the aortic leaflet of the mitral valve; *3*, the fibrous shelf; *4*, the accessory mitral-like leaflets with attached chordae tendineae.

Pathologic Findings.—Gross: The heart weighed 440 grams. The right atrium and tricuspid valves appeared normal. The foramen ovale was closed. The right ventricular muscle was slightly hypertrophied, measuring 0.75 cm. thick. The septal and moderator bands were prominent. The pulmonary valve cusps and orifice were normal as was the pulmonary artery. The pulmonary veins drained into a normal left atrium. The mitral valve leaflets and orifice were not remarkable except for a 4 mm. fibrous nodule at the line of closure of the posterior cusp. There was no thickening or fusion of the insertions of the chordae tendineae. The left ventricle was markedly hypertrophied. Its wall measured 1.7 cm. at its greatest thickness. A fibrous shelf surrounded the outflow tract of the left ventricle, projecting inward at the level of the junction of the muscular and membranous septum (Fig. 4). It was markedly sclerotic, 2 mm. thick, projecting 4 mm. on the septal aspect and 3 mm. on the mitral aspect. The edges were rolled and the undersurface revealed systolic pockets (Fig. 5). The lateral portion of the fibrous shelf was intimately adherent to the base of

the aortic leaflet of the mitral valve. From the septal and mitral margins of the fibrous ring there extended two miniature mitral-like leaflets. The *"septal"* leaflet was triangular, measuring 7 mm. at its base, 1 cm. along each of its free margins, and 2 mm. thick. Several thickened chordae tendineae extended from its free edge and joined chordae of the mitral valve originating from the apex of the anterior papillary muscle. The *"mitral"* leaflet appeared as a fibrous band 4 mm. broad, 10 mm. long, and 2 mm. thick. It was adherent to the junction of the anterior and posterior mitral valve leaflets and chordae tendineae

Fig. 6.—Photograph of the transected heart illustrating: *1*, the fibrous shelf; *2*, the *"mitral"* accessory leaflet with attached chordae tendineae; *3*, the hypertrophied muscular septum deviated to the left; *4*, the subvalvular chamber; *5*, the aneurysmal dilatation in the wall of the membranous septum; *6*, the aortic valve.

Fig. 7.—Photograph of the bicuspid aortic valve from above. Note the partial fusion of the commissures laterally and the nodular projections at the base of the sinuses of Valsalva.

arising from the anterior papillary muscles inserted into its free margin. Although the fibrous shelf presented only slight outflow tract obstruction, protrusion of the rudimentary mitral-like valves, as probably occurred during systole, almost completely occluded its lumen. The muscular septum was markedly hypertrophied and appeared deviated to the left just under the fibrous shelf (Fig. 6). The overlying endocardium was sclerotic. The subvalvular chamber between the fibrous shelf and aortic valves above measured 1.2 cm. long. Its

endocardium was wrinkled and sclerotic. An aneurysmal dilatation, 8 mm. wide and 3 mm. deep, was present in the membranous septum projecting into the right ventricle (Fig. 6). The aortic valve was bicuspid, consisting of an anterior and a posterior cusp with partial fusion of the commissures (Fig. 7). The cusps were thickened (1.5 mm.) and sclerotic. The valve orifice measured 1.2 cm. in diameter. Two firm nodular projections from the aortic wall (5 by 5 by 3 mm. and 4 by 2 by 2 mm.) were present in the posterior sinus of Valsalva, extending onto the valve cusp (Fig. 7). One was also present at the base of the anterior sinus. Both right and left coronary ostia originated anteriorly, appeared normal, and their vessels took a normal course. The proximal, ascending arch and descending thoracic aorta were normal.

Microscopic: Elastic fibers were present in the subaortic fibrous shelf and accessory leaflets. Marked endocardial sclerosis was present in the bicuspid aortic valves, subvalvular chamber, the fibrous shelf, and accessory valves. Foci of chronic nonspecific inflammation were apparent. The nodules in the sinuses of Valsalva and on the mitral valve consisted of laminations of hyalinized fibrous tissue.

DISCUSSION

Congenital subvalvular aortic stenosis was first described by Chevers[7] in 1842 and its embryogenesis outlined by Keith[17] in 1909. A review of the English literature reveals only 82 well-documented cases. In addition, there are numerous reports where the diagnosis has been made clinically,[5, 9, 15, 16, 30, 31] but without surgical or autopsy confirmation.

The usual pathologic morphology[13] consists of a shelf-like ring of fibrous hyalinized tissue in the outflow tract of the left ventricle located at levels varying from the base of the aortic valve cusps to the junction of the membranous and muscular septa. The subvalvular chamber, corresponding to the level of the membranous interventricular septum, shows marked endocardial thickening and sclerosis. The aortic valve cusps appear normal and have a normal valve orifice. The ring of fibrous tissue may be several millimeters thick, with rolled edges and systolic pockets on its undersurface. It may project slightly into the lumen of the outflow tract or almost completely occlude it. The fibrous ring always adheres to and involves the base of the aortic leaflet of the mitral valve. There is generally left ventricular muscle hypertrophy in which the septal muscle partakes and which may consequently appear deviated to the left. Subaortic stenosis has been associated with other anomalies of the aorta (aortic stenosis, bicuspid aortic valve, coarctation, and patent ductus arteriosus)[15, 19, 21, 28] with interventricular septal defect, with aneurysm of the interventricular septum,[23] and with infundibular pulmonic stenosis.[2, 25] The risk of bacterial endocarditis is great and may be the initial presenting symptom.[16, 21, 23, 28, 29]

Keith[17] ascribed the development of subvalvular aortic stenosis to persistence of the ridge separating the embryonic bulbus cordis and the original ventricle. A similar mechanism explains the development of congenital infundibular pulmonic stenosis. Some investigators[8, 11, 16, 20] disclaim this theory and attribute subaortic stenosis to either neonatal or postnatal inflammation. Careful histologic studies by Wigglesworth and others[14, 29] have demonstrated elastic tissue fibers within the fibrous shelf in continuity with the endocardial elastica, which they interpret as indicating the congenital nature of this lesion. However, a

superimposed nonspecific chronic inflammatory reaction may well explain the marked endocardial sclerosis seen in the subvalvular chamber and over the adjacent muscular septum.[14]

The congenital nature of our patient's subvalvular obstruction is readily apparent. The miniature mitral-like leaflets attached to chordae tendineae suggest some relation to embryogenesis of the mitral valves (endocardial cushion defect). The nodular projections of the aortic wall in the sinuses of Valsalva and on the aortic cusps may possibly represent abnormal remnants of the embryonic conal-truncal ridge. The embryogenesis of bicuspid aortic valve has already been established.[1] The mechanism of obstruction in this case was complex. There were definitely two and possibly three contributing factors. The fibrous subvalvular shelf augmented by protrusion of the accessory valve leaflets into the outflow tract during systole presented the main impediment to flow. However, it is conceivable that the hypertrophied muscular septum, in the presence of an oblique subvalvular chamber, also created some degree of functional stenosis during systole.

The cardiac arrest which resulted in the patient's death was no doubt a consequence of hypoxia and decreased cardiac output. Hypoxia developed because of ventilatory restriction secondary to operative trauma and hemothorax. Decreased cardiac output occurred as a result of persistent outflow obstruction, decreased myocardial reserve, and possible hypovolemia. In view of the postmortem findings it is not too surprising that the subvalvular defect was not detected at operation. Since functional stenosis does not present an anatomic obstruction to insertion of the index finger through the aortic valve into the left ventricle, the importance of a careful detailed exploration of the subvalvular area in a dry field becomes apparent. In addition, the presence of a bicuspid aortic valve or other congenital anomaly of the aorta should alert the surgeon to the possibility of subaortic stenosis. Had a completely dry field been achieved in our case, the accessory leaflets might have been visualized and excised.

The clinical differentiation of subvalvular aortic stenosis from valvular stenosis is extremely difficult.[6, 18, 24] The presence of a normal aortic second sound or a dicrotic notch on the arterial pressure tracing is not necessarily diagnostic. Findings suggestive of aortic stenosis, in the absence of a positive history of rheumatic fever, should make one suspect this condition. In a recent operative series reported by Brock,[4] over 80 per cent of patients were under 20 years of age. Positive differentiation of these two types of aortic stenosis may be achieved by left heart catheterization and the demonstration of a subvalvular chamber with lower systolic pressure levels as the catheter passes from left ventricle to aorta or vice versa. The failure to detect the subvalvular chamber in our patient is not readily explained, but this misleading finding, although unusual, has also been encountered by others.[4] Selective angiocardiography has been extremely useful in this type of lesion and may clearly demonstrate the fibrous shelf, the subvalvular chamber, and normal aortic valve cusps and orifice.[23, 27] Accurate preoperative diagnosis enhances the chances of successful surgical attack by precisely localizing the obstruction and aids the surgeon in planning the operation.

Subaortic stenosis can be relieved by either closed[25] or open-heart techniques.[2, 3, 4, 22, 25, 26, 27] In open-heart procedures the stenosis is exposed through an aortotomy incision by retraction of the aortic valve cusps. Incision or preferably excision of the fibrous shelf is then carried out under direct vision. Initially, hypothemia with inflow occlusion was utilized, but the use of the pump-oxygenator (with or without hypothemia) has permitted more careful and complete repairs without time limitations. The use of the pump-oxygenator also enables simultaneous correction of infundibular pulmonic stenosis, if such is present. Closed techniques involve passage of a dilator through a stab wound in the apex of the left ventricle and fracture of the fibrous shelf by gradual dilatation of the outflow tract. Brock has noted similar results using open and closed techniques and prefers closed procedures in severe cases because of their relative brevity and simplicity. No matter which method is used, complete disappearance of subvalvular pressure gradients may not occur in spite of apparent anatomic correction. In some cases, pressure gradients present postoperatively diminish over several months. This finding is explained by persistence of functional muscular stenosis. As muscular hypertrophy subsides, outflow obstruction recedes and the pressure gradient is gradually reduced.[4, 22] A good operative result makes the patient asymptomatic and returns him to normal activity.

SUMMARY

1. A case of bicuspid aortic valve associated with an accessory stenotic subvalvular bicuspid valve is presented, together with a discussion of subaortic stenosis.

2. Although accurate preoperative diagnosis of subvalvular obstruction can usually be made by left heart catheterization and angiocardiography, findings may occasionally be misleading.

3. Subaortic obstruction can be relieved by either closed or open-heart techniques. In open-heart procedures, if gross obstruction is not readily apparent, careful exploration of the left ventricular outflow tract must be carried out in a dry field.

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CORONARY SINUS BLOOD FLOW IN HYPOTHERMIA

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THE CLINICAL use of hypothermia alone or in combination with total cardiopulmonary bypass and extracorporeal circulation necessitates a better understanding of its hemodynamic effects. This report is concerned with a study by direct measurement of coronary sinus blood flow in the hypothermic and normothermic states.

MATERIALS AND METHODS

Mongrel dogs were anesthetized with 5 per cent thiopental sodium administered intravenously. Tracheal intubation was carried out and oxygen delivered rhythmically by means of a mechanical respirator. The operations were done with clean, but nonsterile, technique.

With the animal in the lateral position, a cannula was introduced into one femoral artery and connected by plastic tubing to a U-tube mercury manometer. The right femoral and the right external jugular veins were exposed. A right fourth intercostal space thoracotomy incision was made. The pericardium was opened widely anterior and parallel to the phrenic nerve. The coronary sinus was identified on the right ventricular surface anterior and medial to the inferior vena cava. A variable number of small veins were noted entering this short venous trunk proximal to reception of its main branches. The epicardium was incised in the coronary groove alongside the sinus. It was possible to tunnel underneath the sinus and pass around it a strand of 3-0 silk. In case slight bleeding occurred from the separation of adherent myocardial fibers, hemostasis was easily obtained by applying a sponge or a strip of Gelfoam for a few moments. In most instances this approach permitted isolation of the sinus proximal to the entry of all the small tributaries. The animal was heparinized and a No. 16 Fr. plastic catheter was inserted into the femoral vein. Another No. 14 catheter with two side holes, 0.5 cm. from its tip, was introduced into the jugular vein and passed into the right atrium through the superior vena cava. The catheter was then further manipulated until its distal centimeter lay in the coronary sinus. This catheter was connected by plastic tubing to a siliconed, open, graduated burette from which the blood was led by plastic tubing through the head of a Sigmamotor pump to the catheter in the femoral vein. The extracorporeal tubing and burette were filled with fresh donor blood. When the ligature was tied snugly about the catheter, the total coronary sinus return passed into the catheter. During periods of measurement of blood flow, the pump was stopped and the period of time during which 25 c.c. of blood accumulated in the burette was determined. Otherwise, the pump was utilized to keep the level in the burette constant. Blood flows were

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determined every 5 minutes and seven determinations were made upon each animal. The time required for preparation of the animals ranged from 30 to 60 minutes. The electrocautery was used and blood loss was minimal.

One group of animals had been previously immersed in ice water under thiopental sodium anesthesia until the esophageal temperature had fallen to 33° C. By the completion of the surgical exposure and cannulations, the temperature of these animals had drifted down to a level of about 29° to 30° C.

Both normothermic and hypothermic animals were maintained at the proper temperature by immersion of the measuring burette and the connecting tubing in either warm or cold water baths. The coronary sinus flow was allowed to drain freely for a period of from 5 to 15 minutes before any calculations of flow were made.

TABLE I. DATA ON NORMOTHERMIC AND HYPOTHERMIC ANIMALS

NO. ANIMALS	WEIGHT (KG.)	AVERAGE TEMP. (DEGREES C.)	CORONARY SINUS FLOW (C.C./KG./MIN.) MIN.	MAX.	AVERAGE	AVERAGE B. P. (MM. Hg)	AVERAGE HEART RATE
Normothermic Animals							
1	20	36.5	4.1	5	4.5	150	130
2	19	37	3.1	4.3	3.3	130	140
3	21.1	38	4.3	6.6	5.2	115	130
4	16	37	3.8	4	3.9	120	130
5	20.2	38.5	3.9	5.7	4.9	160	130
6	15.2	37.7	4.4	4.7	4.5	140	132
7	18.1	37.5	2.9	3.5	3.2	150	140
8	19	37	2.0	2.9	2.5	112	130
9	18.1	37.8	2.7	3.2	3.0	160	150
10	19	37.5	2.7	3.1	2.9	160	140
11	12	37.2	6.4	8.1	7.5	70	150
12	15.2	36.2	2.5	3.6	2.8	120	140
13	13.7	38	4.3	5.4	4.9	125	120
14	16.2	37.1	3.7	4.1	3.8	140	140
Hypothermic Animals							
1	17	31	2.1	2.3	2.2	110	65
2	14.1	31.3	1.4	1.6	1.5	75	75
3	16	29	1.3	1.3	1.3	95	95
4	18	30	1.1	1.3	1.2	80	86
5	18	29.5	1.4	1.8	1.6	85	130
6	16.8	30.3	2.4	3	2.7	115	120
7	14.5	30.4	2.4	2.8	2.8	88	100
8	12.5	29.9	3.5	4.2	2.1	100	95
9	15	30.6	1.6	2.4	1.9	90	100
10	19.8	29.9	1.7	1.8	1.8	90	100
Mean Values							
Normothermic	14	37.4	3.3	4.6	4.1	136	132
Hypothermic	10	30.2	1.9	2.2	1.9	96	93

RESULTS

The results are tabulated in Table I. Average values of temperature, blood pressure, and heart rate over a 30-minute period are recorded for each animal. The flow rates listed for each dog are the minimal, maximal, and the average of the seven determinations made. The average temperature of the relatively normothermic animals was 37.4° C., the mean heart rate 136, and the average blood pressure was 132 mm. Hg. In these animals the mean coronary sinus

flows in cubic centimeters per kilogram per minute ranged from 3.3 to 4.6 and averaged 4.1. In contrast, the hypothermic group had an average temperature of 30.2, a mean heart rate of 96, and an average blood pressure of 93 mm. Hg. In them the mean coronary sinus flows ranged from 1.9 to 2.2 and averaged 1.9 c.c. per kilogram per minute. The blood pressure and heart rate in the hypothermic group were approximately 70 per cent of those observed in the normothermic animals, the coronary sinus flow about 46 per cent.

DISCUSSION

It is believed that the method used in these studies is a reliable one for determining total coronary sinus return and under constant conditions measured values in any given animal were easily reduplicated. In studies utilizing the heart-lung preparation, Evans and Starling,[1] Markwalder and Starling,[2] and Anrep, Blalock, and Hammouda[3] all found that the coronary sinus return represented about 60 per cent of the total coronary blood flow. Our experiments demonstrate that cooling the dog to moderately hypothermic levels results in a decrease in coronary sinus flow to approximately 46 per cent of that observed in normothermic animals.

A number of studies have been carried out in experimental animals relating to this problem. In 1929 Anrep and Hausler[4] reported results of studies with heart-lung preparations. They used a hot wire anomometer to measure coronary artery flow, kept the temperature of the systemic blood of the heart-lung preparation constant, and varied the temperature of the blood perfusing the coronary vessels. Their studies indicated that when the coronaries are perfused with cool blood the flow increases and that it decreases upon perfusion with warm blood. On the other hand, the opposite effect was noted when the heart muscle was cooled or warmed. Cooling diminished and warming increased the coronary flow. Two years previously Cruickshank and Subba Rau[5] had studied the effect of cooling and warming isolated arteries. They reached the conclusion that cooling resulted in contraction of systemic and dilatation of coronary arteries. More recently Berne[6] investigated the effect of hypothermia upon coronary blood flow. Cooling was induced by immersion and circumflex coronary artery flow was measured by a rotameter. As was true in our own experiments, the coronary flow was observed to decrease with cooling to moderately hypothermic levels. He observed, however, that in severe hypothermia (about 20° C.) the coronary resistance was actually reduced since artificial elevation of the perfusion pressure resulted in flow values greater than those obtained at identical pressures in the earlier and less severe stages of hypothermia. More recently Hardin and his colleagues[7] have studied the effect of cardiac cooling upon coronary vascular resistance. They used total cardiopulmonary bypass and extracorporeal circulation and maintained the body temperature at normal levels with a heat exchanger. Arterialized blood was withdrawn from the animal, passed through a cooling device and returned by pump into the coronary arteries through the proximal portion of the clamped ascending aorta. A constant rate

of coronary perfusion was used. They found that the perfusion pressure of the beating, but not working, heart of the normothermic animal fell, in most instances, as the heart was progressively cooled. This decreased vascular resistance in the heart perfused with cold oxygenated blood could not be adequately explained by their electrolyte studies of coronary sinus blood or by slowing of the heart rate. They found that the period of cardiac systole was actually proportionately longer in the cooled than in the normothermic heart. They concluded that cooling the heart of the normothermic animal by direct perfusion of the coronary arteries with chilled blood brought about active vasodilatation of the coronary vessels.

The literature, therefore, presents some conflicting data and it is difficult to explain some of the observed differences. There can be no doubt, however, from our observations that there is a marked decrease in coronary sinus return in the dog cooled by external immersion in ice water and allowed to adjust through his own regulatory mechanisms his heart rate, perfusion pressure, etc. This same appears to hold if the animal is cooled by extracorporeal chilling of blood. In 2 dogs cooled by removing venous blood, passing it through a cooling chamber, and returning it by pump into the venous system, the same decrease in coronary sinus flow was observed.

This decrease in coronary sinus flow is of roughly similar magnitude to that which has been found to occur in cardiac output and in renal blood flow in the moderately hypothermic state, judging from other experiments carried out in this laboratory. The coronary sinus flow at roughly 30° C. was approximately 46 per cent of that observed in animals with an average body temperature of 37.4° C. Mean renal blood flow at 30° was 52 per cent of that measured at 36.5° C.[8] The cardiac output at 30° was 48 per cent of that at 37° C.[9] Total hepatic blood flow, on the other hand, at about 28.5° C. was 67 per cent of that measured in animals with an average body temperature of approximately 36° C.[10]

SUMMARY

A satisfactory method for measuring directly total coronary sinus blood flow in the dog has been developed. In animals rendered moderately hypothermic by external body cooling, the coronary sinus flow is slightly less than half that observed in normothermic dogs.

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EFFECT OF MYOCARDIAL ISCHEMIA AT VARYING TEMPERATURES ON LEFT VENTRICULAR FUNCTION AND TISSUE OXYGEN TENSION

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THE OPEN REPAIR of certain cardiac lesions is facilitated by temporarily interrupting coronary blood flow. However, at 37° C., 15 minutes of cardiac ischemia produced marked electrocardiographic changes,[5] pronounced depression of left ventricular work capacity,[30] and persistent damage to myocardial respiration. Since oxygen is probably the most critical metabolic factor,[23] the duration of cardiac ischemia may be safely increased by diminishing cardiac oxygen requirements. Cardioplegic chemicals decrease myocardial oxygen consumption, but these agents have proved detrimental to cardiac metabolism, morphology, and ventricular function after arrest.[15] Currently, hypothermia, which decelerates metabolic processes, is the best method of safely prolonging cardiac ischemia.

Several hypothermic techniques for protecting the unperfused heart have been recommended. Willman and associates[31] and Effler[10] combine potassium citrate arrest with hypothermia to 28° C. Gott and Lillehei[13] also recommend 20° C., but perfuse the coronary arteries intermittently with cold blood. Shumway[25] has reported on canine hearts cooled from 28° to 20° C. with topical cold saline. Myocardial temperatures of 7° to 16° C. with total body hypothermia have been utilized by Johnson and his co-workers.[17] The present authors advocate myocardial temperatures below 10° C. during ischemic cold arrest without total body cooling.[15] Thus, considerable disparity of opinion exists concerning the optimal temperature for ischemic, cardiac hypothermia.

The present study was designed to determine the safe duration for interruption of the coronary arterial circulation at selected temperatures. In 38 dogs perfused extracorporeally, coronary blood flow was suspended for varying periods at myocardial temperatures of 37° C., 28° C., 18° C., and below 10° C.

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The resulting cardiac injury was assessed by pre- and post-ischemic left ventricular function curves. Myocardial oxygen availability before, during, and after ischemia was measured.

EXPERIMENTAL METHOD

Healthy mongrel dogs, weighing between 16 and 23 kilograms, were anesthetized with intravenous thiopental and ventilated mechanically with 100 per cent oxygen. The electrocardiogram was monitored throughout the procedure. Blood, cardiac, and esophageal temperatures were recorded with indwelling thermistors. After a midline sternotomy was performed, the animal was given heparin (1 mg. per kilogram) intravenously. Large venous drainage catheters were introduced through the left femoral and innominate veins and advanced into the venae cavae. The azygos vein was ligated. The arterial perfusion catheter was placed in the left femoral artery. The right femoral vessels were cannulated for dye dilution studies. A catheter in the left atrium was connected to a saline manometer. Decompression of the left atrium was accomplished during bypass via a Y connection in the left atrial system.

Ventricular function studies were obtained at selected left atrial pressures.[24] Cardiac outputs were determined at 10-minute intervals by dye dilution techniques using Evans blue dye.[16] The cuvette densitometer was calibrated daily using a volumetric technique developed by Fox.[11] Mean aortic pressure was recorded via a carotid artery catheter connected to a Statham strain gauge. The left atrial pressure, recorded by the saline manometer, was altered between 8 and 30 cm. saline by transfusing or bleeding the animal.

Myocardial oxygen availability was monitored before, during, and after the ischemic episodes with platinum microelectrodes. These microelectrodes, when inserted into tissue, measure the amount of oxygen reduced at the electrode tip. The microelectrodes respond linearly to the partial pressure of oxygen. All galvanometer readings of microelectrode activity were adjusted to a temperature of 37° C. by means of temperature calibration curves. These calibration curves were derived by inserting the microelectrodes into myocardium immersed in saline solution at several different temperatures.

Calibration factors to convert the galvanometer readings to millimeters of oxygen tension were derived empirically for each microelectrode. However, these calibration factors had a relatively large standard deviation. Therefore, to avoid compounding the standard error, galvanometer readings were calculated as a percentage of the pre-ischemic control determinations and were not converted to millimeters of oxygen tension.

After control ventricular function and myocardial oxygen studies were obtained, extracorporeal circulation was started. Systemic perfusion was maintained between 40 and 70 c.c. per kilogram per minute. A modified Kay-Cross oxygenator, equipped with an efficient temperature regulating unit,[26] was used with a piston-type pumping system.

For studies at 37° C. and at 28° C., the myocardial temperature was regulated by adjusting the systemic blood temperature to the selected level prior to aortic cross-clamping. For studies at 18° C., the blood temperature was lowered to 18° C. prior to aortic occlusion. After occlusion the myocardial temperature was stabilized and maintained by the addition of topical, cold saline. The systemic blood was then rewarmed to 28° C. while the ischemic heart was kept at 18° C. For cold arrest below 10° C., the technique developed in this laboratory was used.[27] Topical 1° C. saline and iced saline slush were added as necessary to maintain a low temperature. These techniques permitted precise control of the cardiac temperature within ±1° C. The esophageal temperature was held at 28° C. during all hypothermic studies.

The ischemic periods varied from 5 minutes to 1 hour. After the ischemic episode, the aortic clamp was released allowing perfusion of the coronary circulation with systemic blood warmed to 37° C. In hearts cooled below 18° C., 40° C. saline was simultaneously

applied to the external surface of the heart. When necessary the heart was defibrillated with electric shock. Fifteen minutes after release of the aortic clamp, circulatory bypass was discontinued. Ventricular function studies were initiated 15 minutes later.

No drugs other than heparin and Nembutal were administered to any animal.

RESULTS

Figs. 1, 2, 3, and 4 present the left ventricular function curves obtained after varying periods of cardiac ischemia at the four selected temperatures. By increasing left atrial pressure, the work load of the heart is increased and thus

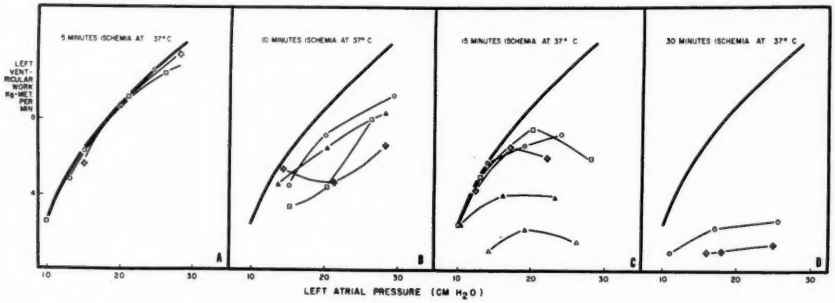
5 MINUTES ISCHEMIA AT 37° C
10 MINUTES ISCHEMIA AT 37° C
15 MINUTES ISCHEMIA AT 37° C
30 MINUTES ISCHEMIA AT 37° C
LEFT VENTRICULAR WORK Kg-MET PER MIN
LEFT ATRIAL PRESSURE (CM H_2O)

Fig. 1.—Effect of ischemia at 37° C. on left ventricular function.

The following groups were studied: 3 animals at 5 minutes, 4 animals at 10 minutes, 5 animals at 15 minutes, and 2 animals at 30 minutes. In this figure and Figs. 2, 3, and 4, the heavy line is a control ventricular function curve determined by averaging the pre-ischemic function curves of 38 animals. Each experimental curve was first calculated as a percentage depression of its individual pre-ischemic control curve. Using these percentages, the experimental curves of each animal were plotted against the control curve *(heavy line)* to facilitate objective comparison.

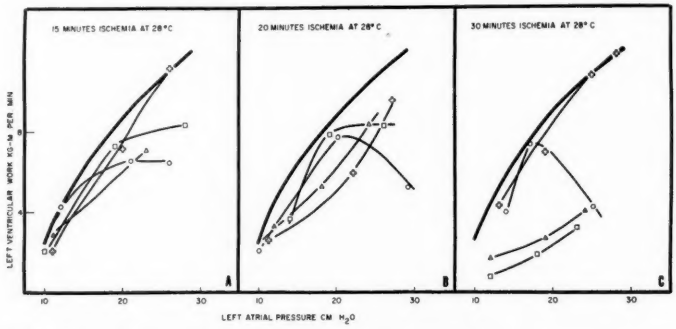
15 MINUTES ISCHEMIA AT 28°C
20 MINUTES ISCHEMIA AT 28° C
30 MINUTES ISCHEMIA AT 28° C
LEFT VENTRICULAR WORK KG-M PER MIN
LEFT ATRIAL PRESSURE CM H_2O

Fig. 2.—Effect of ischemia at 28° C. on left ventricular function.
Groups of 4 animals were studied after 15, 20, and 30 minutes of cardiac ischemia.

the work capacity of the left ventricle may be determined.[24] By comparing the pre-ischemic control curve of each animal to the left ventricular function curve obtained after the ischemic and standard recovery periods, the degree of myocardial functional injury may be assessed.

At 37° C., 5 minutes of cardiac ischemia does not depress the left ventricular work capacity of the canine heart (Fig. 1, *A*). Interruption of coronary flow for 10 minutes depressed myocardial function an average of 25 per cent, but no

function curve was less than 60 per cent of its pre-ischemic control (Fig. 1, *B*). Ischemia for 15 minutes at 37° C. caused profound myocardial functional depression in some hearts, but was well tolerated by other hearts (Fig. 1, *C*). However, every heart unperfused for 15 minutes showed considerable decrease in work capacity at higher left atrial pressures.

Cardiac ischemia for 30 minutes in 2 animals caused functional depression below 30 per cent of control curves (Fig. 1, *D*). In spite of this severe, functional depression, both hearts resumed sinus rhythm and sustained the systemic circulation. However, the electrocardiogram showed persistent changes of anoxic injury, and these hearts became grossly dilated.

The ventricular function curves obtained after 15 minutes of ischemia at 28° C. (Fig. 2, *A*), after 30 minutes at 18° C. (Fig. 3, *A*), and after 60 minutes below 10° C. (Fig. 4) are similar to the curves found after 10 minutes of cardiac ischemia at 37° C. (Fig. 1, *B*). Although most of these curves indicate some decrease in left ventricular work capacity, the post-ischemic function curves at each temperature averaged 70 per cent of the control. Furthermore, no heart performed at less than 60 per cent of pre-ischemic work capacity.

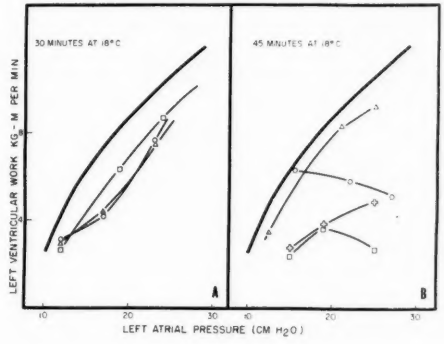

Fig. 3.

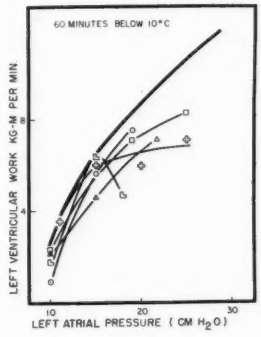

Fig. 4.

Fig. 3.—Effect of ischemia at 18° C. on left ventricular function.
Three and 4 animals were studied after 30 and 45 minutes of cardiac ischemia, respectively.

Fig. 4.—Effect of ischemia below 10° C. on left ventricular function.
Five animals were studied after 1 hour of cardiac ischemia.

Cardiac ischemia for 15 minutes at 37° C. (Fig. 1, *C*), 20 minutes at 28° C. (Fig. 2, *B*), and 45 minutes at 18° C. (Fig. 3, *B*) caused up to a 70 per cent decrease in ventricular work capacity in some hearts. Other hearts were able to tolerate these ischemic episodes without severe loss of function. In fact, these latter hearts were able to perform at work levels comparable to similarly cooled hearts ischemic for shorter periods.

Fig. 5 summarizes over 450 individual myocardial oxygen availability readings. The readings from each heart inscribed a curve. The shaded areas in Fig. 5 are delineated by the extreme curves of each temperature group. As ischemia progressed, these curves diverged. Small changes in the rate of decrease of oxygen availability were barely detectable in the early minutes of

ischemia, but became accentuated with time. Crossing of individual curves within a temperature group was unusual; thus the range of curves probably represents biologic differences in the rate of myocardial oxygen decline.

The effect of temperature on the rate of myocardial oxygen loss is shown in Fig. 6. As temperature was lowered, the slope of the myocardial oxygen curves became more gradual. Furthermore, each curve broke when the

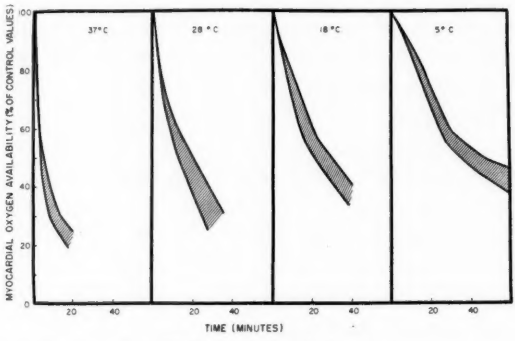

Fig. 5.—Myocardial oxygen availability during ischemia.

The myocardial oxygen availability of each heart was plotted as a percentage of the preischemic control value. All readings were corrected to 37° C. Eight to twenty readings were made on each of 38 hearts. All readings fell within the shaded areas on the above curves.

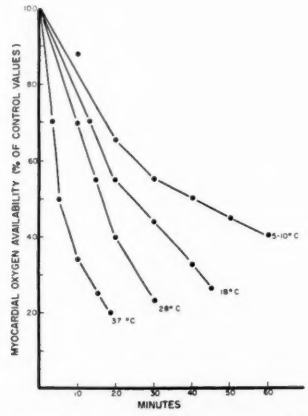

Fig. 6.—Effect of temperature on myocardial oxygen availability during ischemia.

The temperature corrected, myocardial, oxygen, availability readings, graphically presented in Fig. 5, were averaged. The resulting averages were plotted for each of the four selected myocardial temperatures.

myocardial oxygen availability was reduced 45 to 60 per cent. The rate of decline was rapid initially, but decelerated when approximately half of the available oxygen was removed.

Within each temperature group, ischemia of a certain duration—15 minutes at 37° C. (Fig. 1, *C*), 20 minutes at 28° C. (Fig. 2, *B*), 45 minutes at 18° C. (Fig. 3, *B*)—resulted in severe functional depression in some hearts, but relatively little loss of work capacity in other hearts. Tissue oxygen readings below

35 per cent of control values were found in all hearts with more than 40 per cent of functional loss. These depressed hearts apparently utilized tissue oxygen at a faster rate than did the relatively undepressed hearts within the same group. The hearts with less than 20 per cent functional loss were never associated with a tissue oxygen tension below 35 per cent.

DISCUSSION

At 37° C., interruption of coronary blood flow for even short periods causes myocardial damage. The studies presented here (Fig. 1, *B*) confirm the ventricular functional depression resulting from 10 minutes of ischemia noted by Weirich.[30] In 1941, Blumgart[5] found diffuse myocardial fibrosis and persistent electrocardiographic abnormalities after occlusion of the canine left anterior descending coronary artery for 25 minutes. Bryant[6] extended Blumgart's morphologic studies with the electron microscope. He demonstrated mitochondrial and sarcoplasmic reticular swelling in rat myocardium rendered ischemic for 1 hour. Unfortunately, shorter periods of ischemia were not studied. Kardesch[20] found loss of spontaneous action potentials of rabbit and dog myocardial cells after 20 minutes of ischemia at 37° C. Thus, at normothermia, fuctional damage to the ischemic heart occurs within 10 minutes and persistent morphologic damage occurs within 25 minutes.

Metabolic studies confirm the detrimental effects of temporary myocardial ischemia. Bernheim and Bernheim[2] demonstrated that 15 minutes of ischemia at 37° C. resulted in a persistent decrease in the ability of rat heart slices to take up oxygen. Webb, Saunders, and Thienes[29] extended these studies and showed that even 5 minutes of ischemia at 37° C. caused a 36 per cent decrease in rat myocardial respiration. The depressed myocardial respiration persisted for the duration of the experiments (3 to 4 hours). Longer periods of ischemia resulted in more pronounced depression of myocardial respiratory ability.

The exact site of the initial ischemic injury to cardiac metabolism is not known, and the available evidence is conflicting.[2, 9, 14, 20] However, it is established that ischemia for as little as 10 minutes or less causes damage to the heart at 37° C., and that this damage is persistent and may not be reversible.

Hypothermia increases myocardial tolerance to ischemia. The functional studies of this present work confirm this fact. Furthermore, Bernheim and Bernheim[2] found that rat heart slices, ischemic at 5° C. for 30 minutes, could utilize oxygen at control rates after rewarming. Johnson and his colleagues[17] have recently reported survival of dogs which were cooled below 10° C. and were without circulation for 1 hour. Lee and Webb[21] demonstrated that the canine heart refrigerated 6 to 8 hours in 4° C. Tyrode's solution could be successfully transplanted to the neck of a donor animal and could perform work.

During hypothermia, metabolic processes are decelerated in nonhibernating mammals. Work from this laboratory showed that the oxygen consumption of the canine heart approaches zero at temperatures just above freezing.[15] Jude[18] found the oxygen consumption of the working canine heart was reduced to approximately 25 per cent at 20° C. Edwards[8] has demonstrated in the dog that both cardiac oxygen and glucose consumption decreased during immersion

cooling to 26° C. Furthermore, Adolph[1] has presented evidence that profound hypothermia does not interfere with oxygen utilization except by decreasing tissue need for oxygen.

Profound hypothermia to temperatures just above freezing does not injure tissues and is quickly and completely reversible. Juvenelle, Lind, and Wegelius[19] successfully perfused dogs cooled to 12° C. at low flow rates for 3 hours. Gollan[12] obtained survivors after perfusing dogs cooled to 1.5° C. for 1 hour with oxygenated Ringer's lactate solution. Histologic studies have failed to demonstrate morphologic damage to the canine heart arrested 2 hours below 10° C.[28] Numerous investigators have shown that rewarmed hearts are able to utilize oxygen at control rates after profound cooling.[2, 3, 15] Freezing, unless rigorously controlled, injures animal tissue, but profound hypothermia does not.

Although hypothermia decelerates tissue metabolism and thus decreases the rate of oxygen and substrate consumption, the metabolic processes do not cease. Hypothermic as well as normothermic cells may suffer ischemic injury when oxygen and substrate reserves are exhausted.

Determination of post-ischemic ventricular function curves is a sensitive indicator of early ischemic damage. The present experiments document the tolerance of canine myocardium to ischemia at various temperatures. Although animals with over 60 per cent depression in left ventricular function can survive, their postoperative course is jeopardized by this decrease in myocardial functional reserve. In fact, metabolic studies indicate that ischemic damage to aerobic metabolism is persistent and probably permanent. Thus, it is advisable to avoid ischemic injury and the subsequent loss of ventricular work capacity.

Both the ventricular function and the tissue oxygen studies suggest that there is biologic variation within a species in the ability to tolerate ischemia. At 37° C., 28° C., and 18° C., an ischemic period was found which resulted in marked depression in left ventricular function in some animals but relatively little depression in others (Fig. 1, *C*, Fig. 2, *B*, Fig. 3, *B*). Furthermore, tissue oxygen studies demonstrated that hearts at the same temperature varied in the rate of tissue oxygen decrease. Part of this variation may have reflected slight deviation in the exact myocardial temperature, but these were never more than ±1° C.

The tissue oxygen studies of the ischemic cooled heart extend the oxygen consumption studies obtained on the perfused hypothermic heart.[8, 15] A canine myocardial Q_{10} of 2 is confirmed by other experimental data.[13] Similarly, the cooled ischemic heart has a diminished rate of tissue oxygen loss with decreasing temperature (Fig. 6). Initially myocardial oxygen decline was relatively rapid, and probably reflected full aerobic metabolic activity. When approximately half of the available oxygen was gone, the curves broke and the rate of myocardial oxygen decrease became more gradual. This phenomenon was seen at all four temperatures studied and thus probably reflected a cellular adjustment to ischemia. When tissue oxygen decreased below 35 per cent of control values, post-ischemic ventricular function curves failed to equal 60 per cent of control values.

According to these studies, ischemia for 10 minutes at 37° C., 15 minutes at 28° C., 30 minutes at 18° C., and 60 minutes below 10° C. does not inordinately deplete myocardial functional reserve. Furthermore, at these temperatures the indicated durations of ischemia did not result in tissue oxygen tension below 35 per cent. Longer periods of ischemia, however, seriously depressed myocardial functional ability and were frequently associated with tissue oxygen tensions below 35 per cent of control values.

Clinical impressions obtained from patients whose hearts were ischemic up to 71 minutes below 10° C. substantiate the experimental data. Profound hypothermia protects the morphology, metabolism, and work capacity of the heart when coronary blood flow is temporarily interrupted. Thus, this technique offers unique advantages for the surgical repair of aortic valve lesions or ventricular septal defects, and for direct surgery of occlusive disease of the coronary arteries.

SUMMARY

1. Myocardial ischemia of the canine heart for 10 minutes at 37° C., 15 minutes at 28° C., 30 minutes at 18° C., and 60 minutes at 10° C. results in less than 30 per cent decrease of left ventricular work capacity.

2. Myocardial ischemia for longer periods at 37° C., 28° C., and 18° C. was accompanied by pronounced depression of left ventricular function.

3. The decline in myocardial oxygen availability was inversely proportional to the depth of cardiac hypothermia.

4. Myocardial oxygen readings below 35 per cent of control values were consistently correlated with over 60 per cent decreases in left ventricular work capacities.

5. The safe limits of cardiac ischemia at temperatures from 37° C. to below 10° C. are defined.

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AN EXPERIMENTAL AND CLINICAL STUDY OF THE USE OF ACID-CITRATE-DEXTROSE (ACD) BLOOD FOR EXTRACORPOREAL CIRCULATION

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AN ALTERNATIVE to heparinized blood freshly drawn on the morning of operation has been sought by several groups of investigators for use in performing open-heart operations. The use of regular banked blood would have many advantages to those who employ techniques of extracorporeal circulation. A major benefit would be that blood processed for a scheduled heart operation, but unused for one reason or another, would not be wasted. Cross-matching could be done at leisure on blood drawn several days before operation, at the greater convenience of the donors; emergency use of extracorporeal circulation would also be a distinct possibility. The main deterrent to the use of blood stored in ACD anticoagulant solution has been the fear of "citrate toxicity." With the premise that citrate toxicity has its basis in hypocalcemia, or more correctly calcium-binding, it is the purpose of this paper to demonstrate that suitably treated regular banked blood can be used for extracorporeal circulation both experimentally and clinically.

The study is divided into four parts for ease in description, the results being described after each method. The first part deals with in vitro experiments on the clotting of heparinized and ACD blood with various additions of calcium. The second section deals with direct coronary arterial perfusions with "converted" ACD blood in dogs. Third, our experience with whole body perfusions of dogs using converted ACD blood is described. Finally, the results of a clinical trial are presented.

THEORETICAL CONSIDERATIONS

Each unit of citrated blood used experimentally contained 120 ml. of ACD solution B (USP). The composition of ACD solution B is as follows:

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Sodium citrate (USP)	1.58 Gm. (5.37 mM)
Citric acid anhydrous	0.53 Gm. (2.76 mM)
Hydrous dextrose	1.76 Gm.
Water for injection	120 ml.

Total citrate per unit = 8.13 mM

Bunker and his co-workers[10] measured calcium ion concentrations during massive citrate infusions and found that marked cardiac depression was accompanied by a lowering of the calcium ion concentration from the normal 1 mM per liter to less than 0.5 mM per liter. It would appear, therefore, that a calcium ion level of about 1 mM per liter is necessary for adequate cardiac action in the presence of a normal plasma potassium concentration. The ionization of calcium citrate was determined by Hastings and McLean,[17] and, by using their nomogram relating total citrate, total calcium, and calcium ion concentration, one finds that to maintain a calcium ion concentration of 1 mM per liter, in the face of the 16.26 mM per liter of citrate present in ACD blood, the total calcium must be increased to 10.30 mM per liter. Since normal total blood calcium is about 2.5 mM per liter, the added calcium should, therefore, be about 7.8 mM per liter. Thus, on theoretical grounds, the additional calcium must be of the order of 11.5 ml. of 10 per cent calcium chloride solution (0.68 mM of calcium per milliliter) per liter of ACD blood. It should be emphasized that the ionized calcium represents only a small proportion of total calcium. For example, reference to the Hastings-McLean nomogram indicates that the addition to citrated blood of sufficient calcium to raise total calcium from 2.5 to 12.25 mM per liter increases calcium ion concentration only to 1.3 mM per liter. This calcium ionization system should in theory serve as an excellent "buffer" to give wide latitude in the restoration of acceptable calcium ion concentration.

IN VITRO COAGULATION STUDIES

Method.—To 100 ml. aliquots of either fresh heparinized or out-dated ACD human blood, various additions of calcium and heparin were made. The onset of clotting was noted during 24 to 36 hours after the additions. Samples were removed at 1 hour after the addition of calcium and titrated with protamine[30] to determine the quantity of residual heparin.

Results.—Heparinized blood, such as that used for clinical extracorporeal circulation, normally does not clot in less than 24 hours if left at room temperature. Addition of large quantities of calcium chloride will either cause clotting to occur within 1 hour or drastically reduce the protamine titration value. In a typical experiment, blood containing the heparin equivalent of 55 μg of protamine per milliliter titrated at only 10 μg of protamine per milliliter 1 hour after the addition of 2 Gm. per liter of calcium chloride (10 per cent solution).

ACD blood will not clot even if left at room temperature for several days. Firm coagulation occurs, even in old ACD blood, in less than 15 minutes when more than 4.1 mM (0.6 Gm.) of calcium chloride per liter of blood is added.

Heparin can prevent this coagulation for a time, varying with the ratio of calcium to heparin added. For example, ACD blood recalcified with 4.1 mM per liter and with 10 mg. per liter of heparin added will not clot in 1 hour, but will clot in about 24 hours.

Each increase of 0.2 Gm. per liter in the calcium chloride content of ACD blood required the addition of approximately 10 mg. of heparin per liter to prevent coagulation within 24 hours and an additional 10 mg. per liter to prolong the clotting time to 36 hours or more (room temperature).

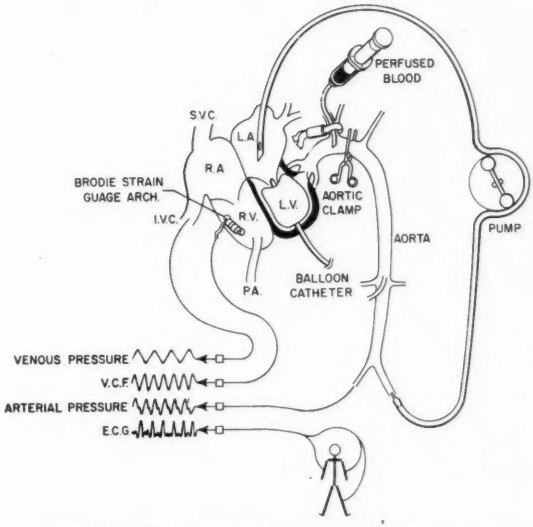

Fig. 1.—Experimental design for intermittent coronary artery perfusion in dogs. Coronary arteries are shown diagrammatically arising from root of aorta. Coronary perfusion is via cannula in right carotid branch of brachiocephalic artery.

When protamine titrations were done 1 hour after the addition of heparin and calcium to ACD blood, the dramatic reductions in residual heparin seen with heparinized blood were not found. Even the addition of 3 Gm. of calcium per liter led to a decrease in heparin equivalent of only 5 to 30 μg of protamine per milliliter. This anomaly can be explained if calcium ion concentration, rather than total calcium, is the determinant of the initiation of the clotting mechanism (see Theoretical Considerations).

CORONARY ARTERY PERFUSION

By direct coronary artery and total body perfusions in dogs we have attempted to arrive at the dosage of calcium which will just nullify the adverse effects of citrate on the myocardium.

Method.—Mongrel dogs were anesthetized with 30 mg. per kilogram of sodium pentobarbital intravenously, and the chest was opened through the third left intercostal space. The right carotid artery was cannulated with a

polyethylene catheter, the tip of which was manipulated to lie within the ascending aorta. The aortic arch was dissected so that an atraumatic arterial clamp could be placed across it for intermittent occlusion distal to the entry of the cannula. Total left circulatory bypass was obtained by a closed pump circuit from the left atrium to the femoral artery. Flow through the left

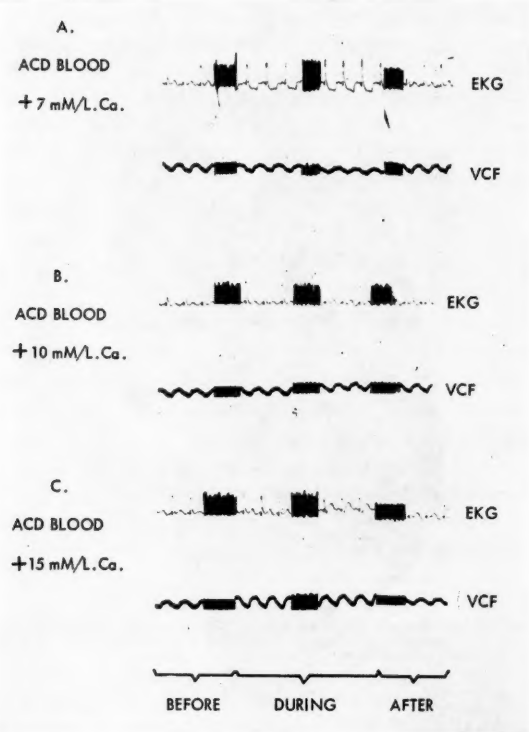

Fig. 2.—Coronary artery perfusion in dogs. Typical tracings obtained with low *(A)*, medium *(B)*, and high *(C)* calcium dosage during perfusions with ACD blood. Example *B* was comparable with perfusion with heparinized blood.

ventricle was prevented by placing an inflatable balloon within the ventricular cavity through a small apical puncture hole (Fig. 1). The extracorporeal circuit was primed with fresh heparinized blood. Ventricular contractile force (VCF) was measured by means of a Walton-Brodie strain gauge arch sutured to the wall of the right ventricle.[6] The electrocardiogram, central venous pressure, and arterial blood pressure were also monitored.

During a coronary perfusion the following sequence of events occurred. The left ventricular balloon was inflated with 30 ml. saline. This caused a sudden drop in blood pressure to near cadaveric levels. Immediately, the left bypass was started and the blood pressure allowed to stabilize. The aorta was then cross-clamped and the injection of 100 ml. of oxygenated blood into the "coronary" cannula was started. The injection was timed to last exactly

1 minute, at which time the aortic clamp was released, the pump stopped, and the balloon deflated in rapid succession. The preparation was then allowed 10 to 15 minutes to recover, and the sequence was repeated as often as good recovery between perfusions occurred.

The perfusates comprised aliquots of either fresh heparinized blood (control) or stored citrated blood to which heparin (5 mg.) and varying quantities of 10 per cent solution of calcium chloride had been added. On each preparation an attempt was made to find the point of balance between "citrate" (or hypocalcemic) depression and hypercalcemic excitation. The various parameters were monitored on a 4-channel direct-writing oscillograph. Examples of the tracings obtained are shown in Fig. 2, *A*, *B*, and *C*.

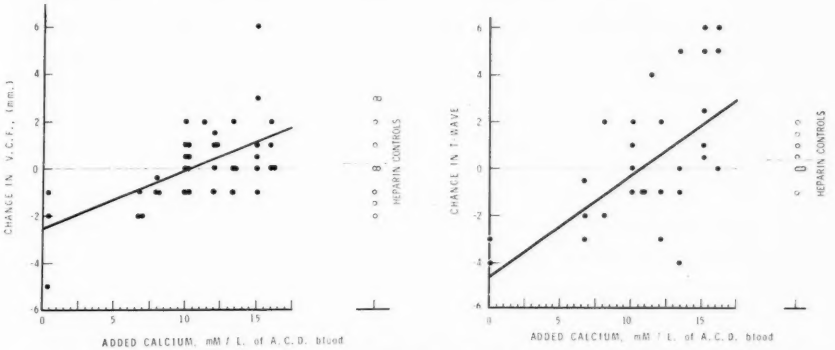
CHANGE IN V.C.F., (mm.)
ADDED CALCIUM, mM / L. of A.C.D. blood
HEPARIN CONTROLS
CHANGE IN T WAVE
ADDED CALCIUM, mM / L. of A.C.D. blood
HEPARIN CONTROLS

Fig. 3.—Change in ventricular contractile force and T wave of electrocardiogram. Scattergrams of data from 8 experiments plotting change in ventricular contractile force *(left)* and T wave of electrocardiogram Lead II *(right)* against addition of calcium (mM/L. of ACD blood).

Results.—In 8 experiments the tracings were technically acceptable and are analyzed in Fig. 3. The changes in VCF occurring during the actual perfusions were measured; the values at the mid-points and end-points were compared with the deflections at the start of the injections. The alterations in electrocardiogram were more difficult to assess numerically, although a general pattern of change emerged as the calcium concentration was varied. This was most clearly manifest in the T wave, in which a change upward (regardless of its initial direction) was taken to indicate excess calcium ion; citrate effect was indicated by a downward deflection. It is fully realized that mechanical factors and anoxia must play a part in the changes in electrocardiogram and VCF, but the effects of heparin controls were reproducible and, therefore, other alterations are attributable to calcium and/or citrate. When the change in contractile force and T waves were plotted against calcium addition, it was seen that there was a range over which responses of VCF and the electrocardiogram were the same or similar, whether heparinized or recalcified ACD blood was used. Isoactivity of calcium and citrate occurred with an average addition of 11.6 mM of calcium per liter of citrated blood. The age of the blood up to 7 days of storage at 2° to 6° C. did not appear to affect the result. Blood kept longer than 7 days was not tested.

Comment.—Contractility was well maintained on perfusion with ACD blood containing 8.2 mM per liter or more of calcium. Increased responses of VCF and electrocardiographic changes characteristic of hypercalcemia were not seen until the addition of 15.0 mM per liter. This preparation was rather unphysiologic because of the admittedly artificial nature of the experiment. This may have resulted in the apparent calcium requirements being somewhat higher than the theoretically calculated amount, which was 7.8 mM per liter.

TOTAL CARDIAC BYPASS

Method.—Ten mongrel dogs, weighing 12 to 28 kilograms, had light anesthesia induced with intravenous sodium thiopenthal. Narcosis was continued by intermittent doses of the same agent or by the introduction of halothane through the intermittent positive pressure respiratory system. Median sternotomy was performed, and the dogs were placed on cardiac bypass using the Kay-Cross rotating disc oxygenator and De Bakey pump system, currently employed clinically in this department. Systemic blood pressure, central venous pressure, electrocardiogram Lead II, right ventricular contractile force, and electroencephalogram were monitored. In the last 4 dogs of the series, whole blood pH, plasma potassium, plasma sodium, plasma hemoglobin, and hematocrit were determined. pH was measured with the Beckman Model H-2 pH meter, using a saline-filled blood-type glass reference electrode maintained at constant temperature (26° C.) in a water bath; values were converted to body temperature by means of the Rosenthal factor.[32] Plasma potassium and sodium were determined with a flame spectrophotometer and plasma hemoglobin by the method of Flink and Watson.[15] The donor blood was converted by the addition of heparin (25 mg. per unit) and calcium. In the first 3 experiments, 9 ml. of 10 per cent calcium chloride solution per unit (12.2 mM per liter) was used. Subsequently, the dose was reduced to 6 ml. of 10 per cent calcium chloride solution per unit (8.2 mM per liter). The citrated donor blood had been drawn from 1 to 14 days before the experiments. Three per cent carbon dioxide was present in the oxygen supplied to the oxygenator during cardiac bypass. Flows of 86 to 120 ml. per kilogram per minute (mean, 103 mg./Kg./min.) were employed for a 20-minute period of perfusion. At the end of perfusion, the dogs were rapidly decannulated and the incisions were closed after insertion of pleural drains. The animals were closely observed for several hours and received additional transfusions of unconverted ACD blood as indicated. The animals were sacrificed and autopsied from 3 to 7 days later. Two control dogs were similarly perfused with fresh heparinized blood.

Results.—All dogs except 1 survived the operative procedure. Of the remainder, 7 lived and were improving when sacrificed 3 to 7 days postoperatively. No gross or permanent neurological changes were apparent. Apathy was seen in 2 dogs for 1 to 2 days; hind limb weakness occurred in 4 dogs for the first day or two, but was probably related to general weakness and bilateral femoral ligations rather than to damage to the central nervous system; 1 dog was thought to have right external strabismus, but this had disappeared

12 hours postoperatively. The dogs which died were (1) a small animal (12.25 kilograms) that showed severe hypotension, coupling, and a grossly abnormal electrocardiogram prior even to cannulation of the venae cavae or administration of any citrated blood. It probably had a considerable overdose of anesthetic agent, and its death shortly after bypass is believed not to be attributable either to perfusion or to ACD blood. (2) Dog No. 7 was found dead in its cage 18 hours after perfusion; no gross cause was found for the death. (3) Dog No. 9 suffered a 13-minute period of superior vena caval occlusion due to buckling of the tip of the caval catheter. This was corrected and perfusion completed, but the animal eventually died. Postmortem examination showed hemothorax.

The electrocardiograms showed no characteristic changes during perfusion. As has been reported by others using heparinized donor blood,[11] transient T-wave inversion was not uncommon during the recovery period. No difference was detected between the two calcium doses in the donor blood in their effects upon the electrocardiogram.

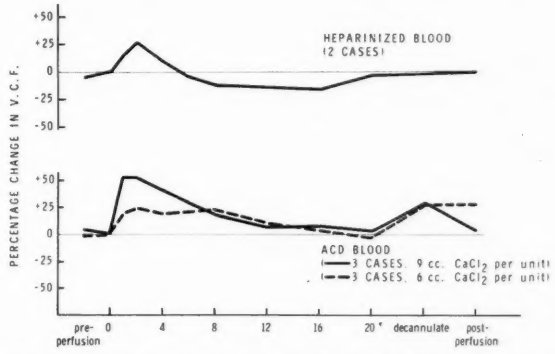

Fig. 4.—Percentage change in ventricular contractile force during extracorporeal circulation in dogs.

The changes in VCF during perfusion are summarized graphically in Fig. 4. The increase in VCF commonly seen in the early period of perfusion with ACD blood also occurred when fresh heparinized blood was used to prime the extracorporeal circuit. Mean values for biochemical data were: (1) Initial pH (7.40) fell immediately to 7.13 with the addition of the highly acid ACD blood (pH 7.06), rising to 7.26 at the end of perfusion, to 7.22 2 hours after, and to 7.24 3 hours after perfusion. Standard bicarbonate followed these pH changes. (2) Plasma sodium remained constant throughout. (3) Plasma potassium, initially 3.06 mEq. per liter, fell to 2.75 mEq. per liter at the end of bypass, but returned to values of 3.15 to 3.20 mEq. per liter 1 to 2 hours, postoperatively.

Comment.—A moderate acidosis at the end of perfusion persisted into the postoperative phase. The figures, however, bear a remarkable similarity to those published for normothermic perfusions with heparinized blood in human beings by McGoon and his colleagues.[23] The only significant change in plasma

TABLE I. COMPARISON OF DATA ON HEPARINIZED PATIENTS (H 1-8) AND PATIENTS PERFUSED WITH ACD BLOOD (ACD 1-10)

CASE	INITIALS	DISEASE OR LESION	WEIGHT (KG.)	SURFACE AREA ($M.^2$)	DURATION OF BYPASS (MIN.)	CARDIAC ARREST (MIN.)	MEAN FLOW (ML./MIN.)	FIBRILLATION DURING BYPASS	SURVIVAL
H 1	F. F. J.	Aortic stenosis, mitral insufficiency and stenosis, tricuspid stenosis	58	1.66	95	48	2,250	+	–
H 2	C. F.	Tetralogy of Fallot	24	0.93	115	61	3,000	–	–
H 3	M. O'C.	Atrial septal defect	44	1.40	10	6	3,000	–	+
H 4	S. T.	Ventricular septal defect	10.3	0.50	34	17	1,100	–	+
H 5	L. G.	Ventricular septal defect	72	1.85	43	22	3,900	–	+
H 6	T. T.	Mitral insufficiency; ventricular septal defect	27.2	0.93	117	65	2,900	+	–
H 7	R. A.	Ventricular septal defect, pulmonic stenosis corrected transposition	56	1.56	94	59	2,500	+	–
H 8	K. H.	Tetralogy of Fallot	14.4	0.61	82	61	1,500	–	+
	Mean		38.2	1.18	74	43.8	2,520	3/8	4/8
ACD 1	G. A.Y.	Pulmonary stenosis	63	1.80	27	8	3,000	+	+
ACD 2	M. W.	Aortic stenosis	62.7	1.72	62	42	4,000	+	+
ACD 3	T. P.	Ventricular septal defect	68	1.90	42	24	4,000	–	+
ACD 4	G. C.	Aortic stenosis	92.6	2.10	75	39	4,500	+	–
ACD 5	R. M.	Pulmonary stenosis	53.5	1.55	28	10	4,000	–	+
ACD 6	R. S.	Ventricular septal defect	53	1.60	30	19	3,500	+	+
ACD 7	K. K.	Atrial septal defect	12	0.55	20	10	2,000	–	+
ACD 8	P. K.	Ventricular septal defect	15.5	0.64	27	10	1,500	+	+
ACD 9	W. L. D.	Atrial septal defect	70.6	1.89	27		4,000	–	+
ACD 10	P. W.	Ventricular septal defect	44.6	1.30	24	10	4,000	+	+
	Mean		53.6	1.51	36.2	17.8	3,450	6/10	9/10

electrolytes was the transient slight decrease in potassium at the end of perfusion. The studies established that survival in dogs was not attended by any undue biochemical disturbances. The next stage was a clinical trial of converted ACD blood in selected patients undergoing operation for intracardiac defects.

CLINICAL TRIAL

As part of a larger study on the clinical use of ACD blood for extracorporeal circulation, an extensive comparison was made between 10 patients in whom the priming volume of the Kay-Cross oxygenator was converted, 1-day-old, ACD blood and 8 patients in whom heparinized blood, also drawn

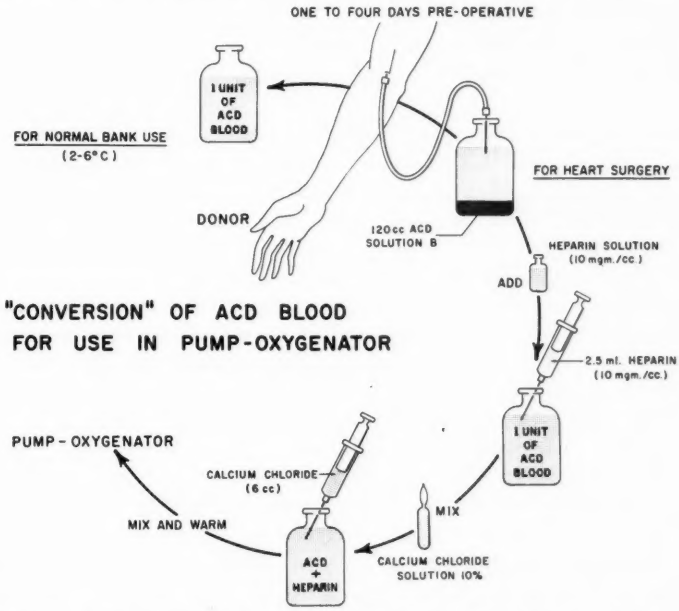

Fig. 5.—Schematic representation of the "conversion" of ACD blood before extracorporeal circulation.

the previous day, was used. The patients chosen for the ACD trial had relatively simple surgical defects unattended by pulmonary hypertension, cardiac failure, or previous operation. Several of the patients in the heparinized group had more complicated congenital defects. Table I gives a summary of data concerning the lesions and perfusions of these patients. The heparinized blood contained 18 mg. of heparin in 30 ml. of diluent per unit; it was drawn 12 to 18 hours before operation and had 1 ml. of 50 per cent glucose added to each unit before rewarming and transfusion. The ACD blood used in this study was also 12 to 18 hours old and contained 120 ml. of ACD solution B (USP) per unit before conversion (Fig. 5). In each unit, 25 mg. of heparin was well

mixed with the blood before the addition of 6 ml. of 10 per cent solution of calcium chloride. The conversion was carried out ½ to 1 hour prior to perfusion. The patients received 1.7 mg. per kilogram heparin before cannulation of the major vessels.

As was the practice of Smith and co-workers[34] in their experimental work with blood stored with Edglugate-Mg, an initial period of 2 to 4 minutes of partial bypass was used to allow gentle mixing of the donor and recipient bloods. Flows of about 2.2 L. per square meter of surface area were maintained throughout perfusion. Three per cent carbon dioxide in oxygen at a flow rate of 10 L. per minute was supplied to the (adult) oxygenator, the temperature of which was maintained at approximately 35° C. by a heating wire coil. At the end of extracorporeal circulation, heparin was neutralized with protamine. The standard dose was 2.5 mg. per kilogram, given in 2 doses. Additional protamine (0.5 mg./Kg.) was administered if protamine titrations 15 minutes after the second dose showed any excess circulating heparin.

The two series were investigated in a similar manner. The parameters monitored were arterial blood pressure, central venous pressure, electrocardiogram, electroencephalogram, plasma potassium, plasma sodium, plasma hemoglobin, and arterial whole blood pH. pCO_2 was determined by the methods of Astrup[4] and Pierce[31] and their associates and, using the Astrup nomogram, values for standard bicarbonate were found. All values for pH and pCO_2 were corrected to the temperature of the blood at the time of withdrawal, using the Rosenthal factor[32] and the line diagram of Bradley and his co-workers,[7] respectively. Some results were checked by duplicate measurements using Van Slyke's manometric method and close agreement was demonstrated (pCO_2 checked within 2 mm. Hg). Plasma chlorides were obtained by the method of Kingsley and Dowdell.[20] Hematocrit, white cell counts, Rees-Ecker platelet counts, and Lee-White clotting times were done by standard clinical laboratory methods before and after operation. Postoperative bleeding was tabulated from the records of chest tube drainage and radiologic evidence was used to exclude the retention of large volumes of blood within the thoracic cavity.

All 10 patients in whom ACD blood was used survived the operative procedure but 1 patient died 13 days postoperatively of massive gastrointestinal bleeding from an acute peptic ulcer. He failed to regain normal consciousness after technically successful relief of severe calcific aortic stenosis. The breakdown of the general data on the 18 patients is given in Table I, and the results of the hematologic and biochemical studies in Figs. 6, 7, and 8.

Acid-base Balance.—For a complete evaluation of acid-base balance, pH, pCO_2, and standard bicarbonate determinations[4] are charted (Fig. 6). The notable differences in these parameters occurred in the first few minutes of partial bypass, i.e., during the phase of mixing of donor and recipient bloods. When mixing was complete, the mean values in the 2 series were closely comparable, and this similarity extended into the postoperative period. The pH at the end of perfusion was normal in both series, associating a mild metabolic

acidosis with a moderately low pCO_2 (about 24 mm. Hg). The close similarity of the two groups and the final normality achieved 24 hours postoperatively was most clearly discernible in the graph of standard bicarbonate.

Plasma Electrolytes (Fig. 7).—There was a consistent decrease in plasma potassium during perfusion in the ACD series; the difference between the 2

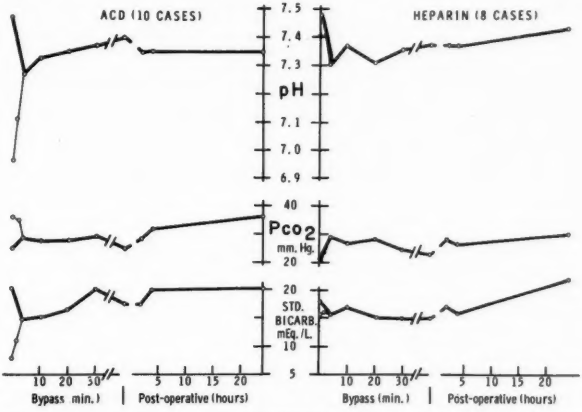

Fig. 6.—Biochemical comparison of heparinized and ACD blood in extracorporeal circulation. *Fine line* indicates values in donor blood prior to extracorporeal circulation and during mixing with the patient's blood.

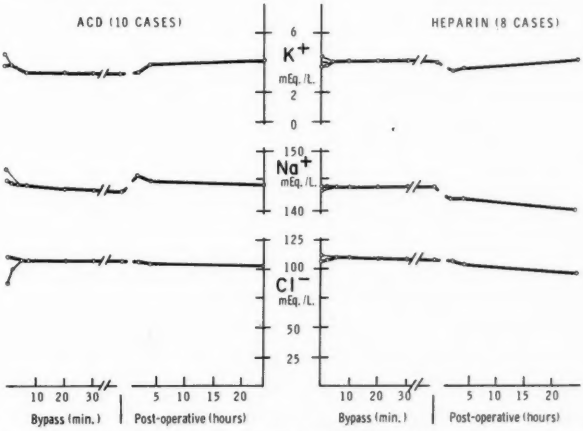

Fig. 7.—Biochemical comparison of heparinized and ACD blood in extracorporeal circulation and during mixing with the patient's blood.

groups was approximately 1 mEq. per liter in the sample taken from the oxygenator at the end of the intracardiac procedure. Again, this divergence very quickly disappeared and, in the remainder of the period of observation, close similarity was seen. Changes in plasma potassium very frequently mirror alterations in pH; a change to a lower pH being accompanied by a rise in potassium and vice versa.[26] Since there was a major shift of pH from 6.96 to 7.40

in the ACD blood during perfusion, a fall in potassium might be expected in this circumstance. No electrocardiographic abnormalities suggestive of hypokalemia were observed associated with this minor fall in plasma potassium.

There was no statistically significant change in plasma *sodium* in either series. (Heparinized cases: from 144 ± 5.3 prior to bypass to 140 ± 10.2 mEq./L.; ACD cases: from 145 ± 8.1 to 144.4 ± 6.7 mEq./L. 24 hours after bypass.)

Plasma chlorides were low in ACD blood with a mean of 87 ± 4.3 mEq. per liter, mainly due to dilution. Measurements during perfusion indicated rapid restoration to normal. During the first 24 postoperative hours, there was a decrease in plasma chlorides which was three times as great in the heparinized group (14.0 ± 5.66 mEq./L.) as in the patients perfused with ACD blood (4.0 ± 5.5 mEq./L.).

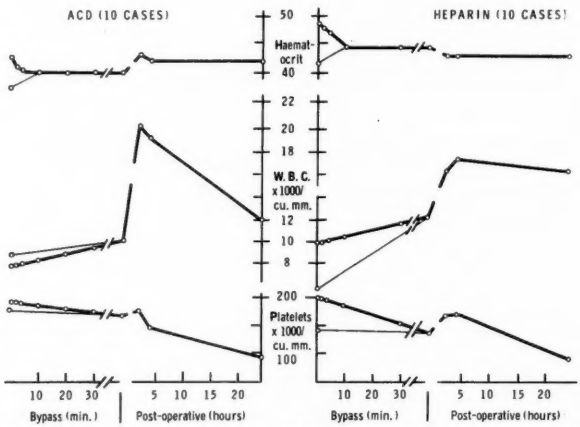

Fig. 8.—Hematologic comparison of heparinized and ACD blood in extracorporeal circulation. *Fine line* indicates values in donor blood prior to extracorporeal circulation and during mixing with the patient's blood.

Hematologic Data.—In the formed elements of the blood, the same patterns of change emerged in both groups (Fig. 8). As mixing of donor and recipient bloods occurred, *hematocrit* assumed an intermediate value in both series. During the next 6 days there was a gradual decline in hematocrit (not shown in graph) by a mean of 5 in the heparinized cases and 4 in the ACD cases. A postoperative *leukocytosis* already well marked 2 hours after the end of perfusion, occurred in patients perfused with ACD blood and controls alike. Counts of over 30,000 per cubic millimeter were seen on occasion. By the end of 24 hours, a return toward normality was already in evidence. The *platelet counts* on donor blood were higher in ACD blood (180,000 ± 29,000/mm.^{3}) than in heparinized (141,000 ± 26,900/mm.^{3}), which is a statistically significant difference. The counts at the end of perfusion showed a minor decrease in both series. Twenty-four hours later, there was a decrease to about 90,000 per millimeter^3 in each series. In no patient perfused with ACD blood did *plasma hemoglobin* rise above 60 mg. per cent by the end of perfusion (mean, 32 mg.

per cent). Hemolysis was initially greater in heparinized blood and rose to higher levels (mean, 150 mg. per cent) at the end of bypass. Lee-White *clotting times* taken before and after operation failed to show a significant difference between the groups.

Postoperative bleeding was tabulated from the records of chest-tube drainage. Fig. 9 summarizes the findings in the series of patients perfused with ACD blood compared with 10 patients of comparable weights and lesions operated upon currently in this clinic using heparinized blood. The figures reflect both blood and pleural transudate. The average drainage in the heparinized group was significantly higher at all times than in the ACD group. The time during which the observations were made varied between 15 and 34 hours postoperatively, with an average of 24.4 hours. It will be seen that the total

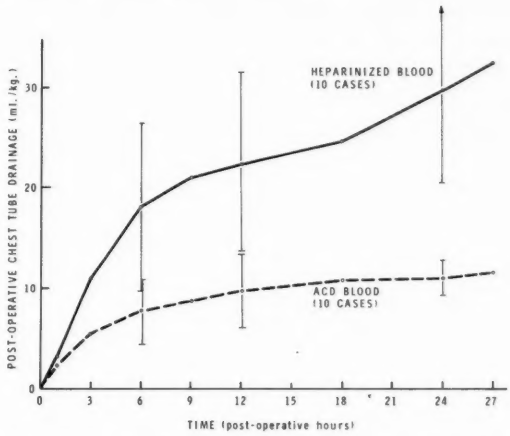

Fig. 9.—Chest tube drainage after extracorporeal circulation. Vertical lines represent one standard deviation.

quantity of drainage from the heparinized patients was more than double that in the patients perfused with ACD blood. Random measurements of plasma fibrinogen and prothrombin time in the ACD cases were within normal limits.

Electrically Recorded Data.—No differences were noted in the electrocardiogram, electroencephalogram, systemic arterial pressure, or venous pressure in the 2 series.

DISCUSSION

There can be little argument with the fact that blood collected immediately before operation with heparin as the sole additive is the most physiological medium for extracorporeal circulation. It has normal pH and electrolyte concentrations, fully viable erythrocytes, and, presumably, an intact quota of factors necessary for coagulation. Storage for longer than a few hours in any anticoagulant mixture, however, results in changes in each of these modalities, to a degree varying with the actual process employed.

On the combined counts of (a) post-transfusion red cell survival, (b) rate of increase in plasma potassium, (c) spontaneous hemolysis, and (d) persistence of clotting factors V, VII, and antihemophilic globulin, acid-citrate-dextrose solution is demonstrably superior to all other preservative mixtures in common use, especially if the blood is collected in plastic containers.[16] The only agent claimed to give equivalent erythrocyte preservation during the first week of refrigeration storage at 2 to 6° C. is the Edglugate-Mg mixture of Smith and his colleagues.[34] However, in common with blood stored in heparin-dextrose solution,[1, 21] alkaline citrate mixtures,[22, 25] and EDTA alone,[24, 35] or decalcified by passage across a cation exchange column, rapidly mounting plasma potassium levels are seen with Edglugate-Mg blood. High plasma potassium values occur only after prolonged storage with ACD.[26] Safe levels of potassium (less than 7 mEq./L.) are found for the first 5 days after collection. There is also some suggestion in the literature that clotting factors are less well preserved by all the above processes than by ACD.[24, 34, 39] The presence of these coagulation factors may account for the decreased postoperative bleeding in the ACD series.

There would appear to be 5 main objections to the use of ACD stored blood for very large and rapid transfusions and perfusions: (a) "citrate intoxication," (b) acidity, (c) dilution, (d) salt-loading, and (e) defective gas transport by the transfused cells.[36] It is with the first of these objections that this paper mainly deals, but some data and considerations pertaining to the second, third, and fourth factors are also presented. The fifth factor (e) is not important until storage exceeds 1 week.

Numerous studies have demonstrated the myocardial "toxicity" of citrate.[2, 3, 8, 14, 18, 19, 38] The effects of massive intravenous and intra-arterial infusions of sodium citrate and citrated blood on systemic and pulmonary arterial pressures, central venous pressure, and electrocardiogram have been investigated, and the findings are well summarized by Moore.[27] Profound hypotension and even ventricular fibrillation can be produced, provided the injection of citrate is large enough and rapid enough. One can only administer large quantities of citrated blood by virtue of the oxidation of its citrate, ultimately to bicarbonate, by the muscles, kidneys, and liver, and by the initial buffering of its acidity by the large extracellular compartment of the body fluid. That the pharmacologic effects of citrate on the cardiovascular system can be combated on a quantitative basis by the prior or simultaneous intravenous administration of calcium salts is illustrated by the experiments of Firt and Hejhal[13, 14] and Nakasone and associates.[28] Our first series of experiments showed that this was true even when large quantities of ACD blood were perfused rapidly and directly into the coronary arteries of dogs. Administration of calcium and citrate was truly simultaneous by actual mixing prior to perfusion. Clotting was prevented by the previous addition of heparin.

Many other points have been brought out as the data were presented, but some re-emphasis may be helpful. After the first few minutes of partial bypass, during which equilibration of the donor blood with the patient's blood volume and extracellular fluid space was taking place, the over-all picture was one of

close similarity between the ACD and heparin groups. The period of partial bypass has theoretical value, especially with the use of older blood, in allowing the body to act as a giant acceptor of excess potassium and hydrogen ions. The initial acidity of ACD is a small disadvantage. The rapid return of pH and plasma standard bicarbonate to figures comparable to those of the control series confirmed the reports in the literature that large transfusions of citrated blood have only minor and transient effects on acid-base balance.[40] Because of this fact, it is, at present, considered that correction of the acidity of ACD prior to perfusion, as suggested by Beer[5] and Bücherl,[9] is probably not necessary. If sodium bicarbonate were used to correct pH and standard bicarbonate to normal, the net effect would be to increase the sodium load. It would seem wise to avoid the addition of what amounts to several hundred milliliters of "saline" in patients with cardiac problems. In infants and small children, the degree of metabolic acidosis seen during perfusion with both ACD and day-old heparinized blood may be undesirable because of the limited buffering power of their extracellular fluid space. In these patients, truly fresh, well-buffered blood would be the perfusion medium of choice.

A few minor differences were seen in the plasma electrolytes, but they are not believed to be clinically significant, i.e., they do not require correction by appropriate intravenous therapy. The hematologic findings are of interest, not only in respect to the similarity between the 2 groups, but because they clearly show the reactions of leukocytosis and thrombocytopenia demonstrated by Pepper and Lindsay[29] to be nonspecific responses to any major surgical trauma.

In a larger study of the clinical use of ACD for extracorporeal circulation, converted blood up to 4 days old has been used with precisely similar results. ACD has been used in over 30 patients to date, including several in whom direct coronary perfusion has been employed. The patients chosen for detailed investigation using ACD blood had relatively simple surgical defects. As it turned out their mean weight (53.6 Kg.) was greater than that of the heparinized group (36.4 Kg.). The selection was done for ease of evaluation, but implies that in the ACD group the ratio of patient's blood volume to priming volume was high compared to that of the heparin series. The differences in lesion (Table I) led to the higher mortality, perfusion time, and hemolysis in the heparinized series.

Several thousands of patients have had cardiac operations in which heparinized blood was used. Any change from this practice merits close scrutiny, and it is hoped that all those who may choose to employ ACD blood for extracorporeal circulation will make careful studies of the patients in order that unanticipated difficulties may be brought to light. In our series of over 30 patients there have been no unusual complications associated with the use of converted ACD blood. ACD blood can, therefore, be recommended for use in circumstances other than those mentioned above (patients with limited acid-buffering power). Its use could also be extended to emergency use of the pump in a variety of conditions of the heart and great vessels.

SUMMARY

1. Blood stored in acid-citrate-dextrose solution for up to 4 days has been used exclusively for clinical extracorporeal circulation.

2. Citrate intoxication, which has its basis in calcium binding, is counteracted by addition of 25 mg. of heparin as anticoagulant and 8.2 mEq. of calcium (as 6 ml. of 10 per cent solution of calcium chloride [USP]) to each unit of ACD blood containing 120 ml. of ACD solution B (USP).

3. Extensive biochemical and hematologic data are presented in a comparison between 2 groups of patients in whom 1-day-old heparinized and "converted" ACD bloods were employed, respectively.

4. The uses and limitations of the method are discussed.

The authors wish to express their appreciation to Dr. Eugene Adashek, Miss Ruth Lokey, and the other staff members of the American Red Cross Regional Blood Center, Los Angeles, for their assistance in this study and for their service to the patients of this institution.

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PHYSICAL FACTORS RELATING TO GAS EMBOLISM IN BLOOD

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With the Technical Assistance of David Ferguson

THE VOLUME of oxygen and carbon dioxide held in physical solution in blood is increased as temperature is decreased. The data of Sendroy and associates[1] indicated that blood that had been equilibrated with oxygen at 20° C. and a pressure of 760 mm. Hg contained in physical solution 34.5 ml. of oxygen per liter of blood. An oxygen tension of 1,121 mm. Hg was required to hold this volume of gas in solution at 37° C.

The extensive studies of Harvey and associates[2] on decompression sickness defined the conditions under which gas emboli could be formed according to the equation $\Delta P = T - P$, which stated that when gas tension exceeded local absolute hydrostatic pressure, physical conditions favored the release of gas from solution.

Thus when blood that has been equilibrated with oxygen at a low temperature is warmed, the formation of gas bubbles is possible whenever the tension of the gas in the blood exceeds the local hydrostatic pressure. The following studies were undertaken to determine how far this formula applied to blood equilibrated with oxygen in an extracorporeal circuit, and to investigate the effects of perfusing the brain in dogs with blood potentially able to release gas emboli.

METHODS

In vitro studies were carried out with the perfusion system represented in Fig. 1. Blood at 20° C. was circulated through the entire apparatus for 1 hour to ensure removal of any air that had been trapped during the filling process. In most instances oxygen was used as the equilibrating gas in order to simplify calculations, and analysis of expired air from the perfused dog's lung yielded concentrations of nitrogen and carbon dioxide that together totaled less than 1 per cent. The tension of oxygen (pO_2) in the blood, the temperature, and

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the hydrostatic pressure were measured at the inlet to and outlet from the heating unit. Gas-tension and temperature calibrations of the Clarke pO_2 electrodes were carried out immediately after each experiment. When bubbles formed, they were easily visualized as they ascended in the bubble-trapping chamber.

Four groups of experiments were made under various conditions. The first group consisted of 11 experiments in which, after the initial hour of circulation, the temperature in the lesser circuit was slowly raised to 37° C., while the temperature in the circuit through the dog's lung was kept at 20° C. After a period of observation at this sustained temperature differential, either the temperature in the lesser circuit was reduced to 20° C. or that in the circuit through the dog's lung was raised to 37° C.

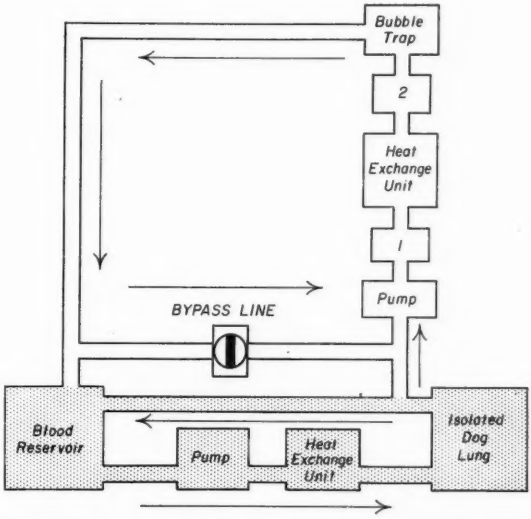

Fig. 1.—Block diagram of perfusion circuit. The pO_2 electrodes and the temperature-recording units are inserted into the blood-flow line of the lesser circuit at positions *1* and *2*. The main or dog-lung circuit is shown *stippled*. (From Donald and Fellows, S. Forum 10: 589-592, 1960.)

The second group consisted of 6 experiments in which, after the initial hour of circulation at 20° C., the lesser circuit was isolated by means of its bypass line, and blood was recirculated solely in this circuit while its temperature was rapidly raised to 37° C. Observations at 37° C. were continued for approximately 1 hour. Two experiments of this type were conducted with the use of plasma in place of blood. In one experiment the blood was initially circulated at 37° C., and this temperature was maintained during the period of recirculation within the isolated lesser circuit.

In a third set of experiments the lesser circuit was replaced by a 70-cm. vertical length of glass tubing with an internal diameter of 0.4 cm. or by paired conical flasks of 250-ml. capacity, one of which contained about 50 ml. of small glass beads. After an hour of recirculation through these units with blood at

26° C., flow was stopped, and the upper ends of the flasks or glass tubing were disconnected from the perfusion tubing and attached to a vacuum system. The blood in these containers was then exposed to various degrees of subatmospheric pressure.

In vivo experiments were performed in 10 dogs. Blood was withdrawn from the femoral artery and led into the isolated dog-lung perfusion circuit, where it was equilibrated with a gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide before being returned to the body via both carotid arteries. Perfusion of the head of the dog was carried out with this system for 95 minutes, both vertebral arteries being temporarily occluded during the period of perfusion.

TABLE I. MEASUREMENTS OF GAS TENSION, TEMPERATURE, AND HYDROSTATIC PRESSURE AT THE TIME OF STEADY, SUSTAINED PRODUCTION OF GAS BUBBLES

EXPERIMENT	SITE OF OBSERVATION	HYDROSTATIC PRESSURE = P (MM. Hg)	TEMPERATURE (°C.)	($pO_2 = T$ (MM. Hg)	CALCULATED pO_2*	$\Delta P = T-P$ (MM. Hg)	Δ TEMPERATURE (°C.)
1	Inlet	820	22.2	653		−167	
	Outlet	744	37.6	828	923	+84	15.4
2	Inlet	850	21.4	730		−120	
	Outlet	776	37.5	796	961	+20	16.1
3	Inlet	850	18.9	733		−117	
	Outlet	776	33.9	825	942	+49	15.0
4	Inlet	838	21.7	687		−151	
	Outlet	761	35.5	856	903	+95	13.8
5	Inlet	816	20.4	695		−121	
	Outlet	736	33.3	895	936	+159	12.9
6	Inlet	806	21.7	650		−156	
	Outlet	758	39.3	854	968	+96	17.6
7	Inlet	810	20.3	711		−99	
	Outlet	761	35.4	856	1004	+95	15.1
8	Inlet	836	21.3	675		−161	
	Outlet	760	34.4	912	912	+152	13.1
9	Inlet	832	19.6	642		−190	
	Outlet	760	38.0	829	922	+69	18.4
10	Inlet	826	21.6	679		−147	
	Outlet	762	29.4	749	816	−13	7.8
11	Inlet	810	20.2	704		−106	
	Outlet	761	39.1	857	1081	+96	18.9
Average values	Inlet	827	20.9	687		−140	
	Outlet	760	35.8	842	943	+82	14.9

*pO_2 was calculated from inlet pO_2 and temperature; it was assumed that there was no loss of gas from the blood.

The carotid cannulas were then withdrawn and hexadimethrine bromide (Polybrene) was administered to counteract the effect of the heparin used during perfusion. Measurements were made of the rate of flow, temperature, and gas tension of the blood entering the carotid arteries. Systemic arterial and central venous blood pressures were recorded by strain-gauge manometers. Blood pressure in the carotid arterial system was recorded by means of a small catheter inserted into the superficial temporal artery.

Five dogs were perfused with blood that was equilibrated with the gases in the isolated dog-lung circuit at 36° C. In 5 animals the blood was equilibrated at 20° C., the blood being rewarmed to 36° C. just prior to being admitted to the carotid arteries.

RESULTS

In Vitro Experiments.—

1. *Effect of slowly increasing the temperature differential in blood equilibrated with oxygen at 20° C.:* Results representative of the 11 experiments of this type are shown in Fig. 2. In this experiment gas bubbles were first seen at a temperature differential of 14.9° C. (36.4°-21.5° C.). Calculation of $\Delta P = T - P$ showed ΔP to be positive and to exceed P (measured at the heater outlet) by 63 mm. Hg. (See Table I for explanation of formula.) When the

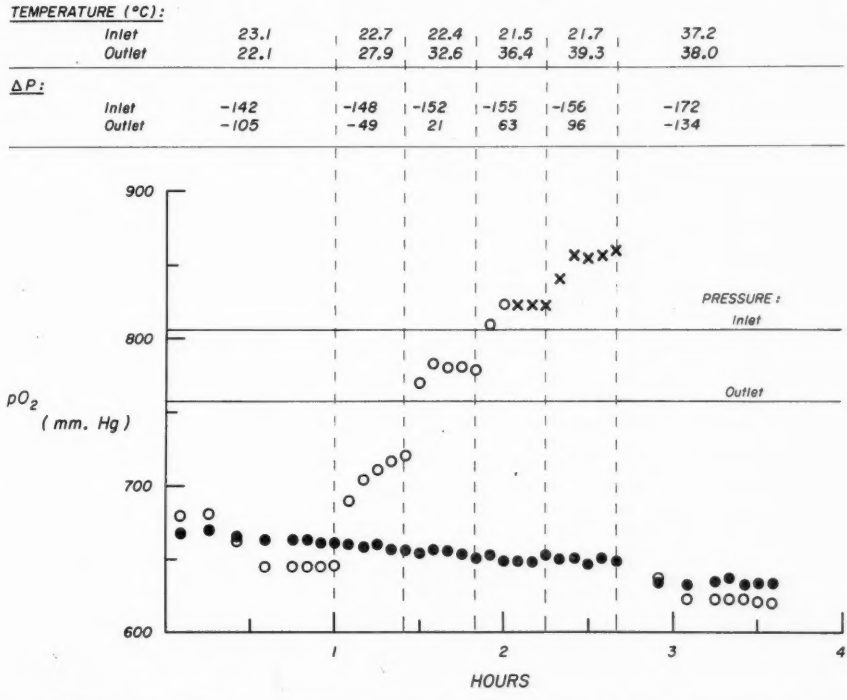

Fig. 2.—Blood-gas tension, temperature, and hydrostatic pressure during successive graded temperature differentials.

Symbols: ● = pO_2 recorded at inlet to heating unit; ○ = pO_2 recorded at outlet to heating unit; and X = gas bubbles recorded in bubble-trapping chamber. (From Donald and Fellows, S. Forum 10: 489-592, 1960.)

temperature differential was maintained at 17.6° C. (39.3°-21.7° C.), a steady, sustained release of gas bubbles was observed. When the temperature in the circuit through the dog's lung was raised to 37° C., thereby abolishing the temperature differential, the production of gas bubbles ceased. Gas tension fell to approximately equal values of 634 and 624 mm. Hg, measured at the inlet and outlet, respectively. When the temperature differential of 17.6° C. was reinstituted, gas bubbles again appeared in a steady stream.

The steady production of gas bubbles at a sustained temperature differential of 18° C. (38°-20° C.) was noted in all experiments, but considerable variability existed with regard to the calculated value of Δ P at which bubbling first began. Details of the 11 experiments are given in Table I. The experiments yielded an average critical Δ P value of 82 mm. Hg and an average temperature differential of 14.9° C. Part of the difficulty lay in confirming the genesis of the first bubble to be observed.

2. *Effect of rapidly increasing the temperature differential in blood equilibrated with oxygen at 20° C.:* When, in 3 experiments, a temperature differential of 17° C. (37°-20° C.) was instituted as rapidly as possible (average 6 minutes), a lag of 1 to 4 minutes occurred before the appearance of the first bubble, and of 5 to 13 minutes before the steady, sustained production of bubbles.

In 6 experiments in which the subsidiary circuit was isolated by means of its bypass line after 1 hour of circulation at 20° C., the temperature was raised from 20° C. to 37° C. in 4 to 10 minutes. Circulation of blood through the heating unit and bubble trap at 37° C. was allowed to continue for 1 hour, but no bubbles were observed. When the heating began, the oxygen tension rose rapidly and reached an average peak value of 850 mm. Hg in 5 to 10 minutes, from which point it declined steadily to a final average value of 677 mm. Hg. Similar results were obtained in the two experiments in which plasma was used instead of blood, with the exception that the peak pO_2 values were higher, and in each experiment a small number of gas bubbles were observed when the temperature of the isolated circuit was raised to 37° C. In the single experiment (experiment 9, Table II) in which the lesser circuit was isolated after the initial circulation of blood at a temperature of 37° C., a fall in oxygen tension was observed during the period of recirculation. Details of these experiments are given in Table II.

TABLE II. EFFECTS OF RAPID REWARMING OF BLOOD THAT HAD BEEN EQUILIBRATED WITH OXYGEN AT 20° C.

EXPERIMENT	CONTROL PERIOD pO_2 (MM. Hg)	CONTROL PERIOD TEMPERATURE (° C.)	PEAK pO_2 (MM. Hg)	pO_2 AT 37° C.* (MM. Hg)	FINAL pO_2 (MM. Hg)	FINAL TEMPERATURE (° C.)	VOLUME OF BLOOD IN CIRCUIT (ML.)	VOLUME OF GAS LOST† (ML.)
1	701	24.9	791	772	724	37.8	400	2.56
2	681	20.1	895	830	770	36.7	400	2.76
3	680	18.4	909	833	765	36.6	500	4.1
4	668	19.3	860	827	717	37.1	500	4.3
5	703	20.4	828	775	548	38.6	600	8.6
6	705	20.4	814	753	538	38.6	600	9.3
Average	656	20.6	850	798	677	37.6		
7‡	670	20.6	960	960	708	38.4	490	4.16
8‡	660	20.1	962	932	619	38.4	490	4.9
9	656	36.8	—	—	150	37.0	375	5.91

*pO_2 at 37° C. was the gas tension observed when the temperature at the pO_2 electrode first reached 37° C.

†The volume of gas "lost" during recirculation was calculated from the difference between initial and final pO_2, the appropriate solubility coefficient, and the volume of blood in the isolated circuit.

‡Plasma was used in experiments 7 and 8, whole blood in the others.

3. *Effect of alteration in hydrostatic pressure in blood equilibrated with oxygen at 26° C.:* Two sets of experiments were performed with flasks and 2 with the 70-cm. glass tubing. A mixture of 95 per cent oxygen and 5 per cent carbon dioxide was used as the equilibrating gas in these experiments. The average temperature of the blood was 26.3° C. (range 25.9° to 26.6° C.) and the average pO_2 was 667 mm. Hg (range 647 to 692 mm.). The pO_2 as measured by the Clarke electrodes agreed within 3 per cent with the tension calculated from the equilibrating gas mixture.

In a series of tests with each type of unit, the average reduction in pressure at which the steady production of bubbles was observed was 150 mm. Hg. The scatter of values, however, was greater than in the experiments in which the temperature was changed. At a vacuum pressure of 150 mm. Hg, bubbles appeared earlier and in greater profusion in the flasks containing the glass beads than in the flasks without beads. The addition of beads to a flask not containing beads and its immediate exposure to a vacuum pressure of 150 mm. Hg resulted in bubbles of gas appearing earlier and in greater number than was the case when the blood-filled flask without beads had been exposed to this same vacuum pressure.

Irrespective of the unit used, if the Tygon connecting tubing was repeatedly clamped with forceps or rhythmically compressed with the fingers during exposure of the blood to a vacuum pressure of 100 mm. Hg, there was an immediate production of clouds of fine bubbles, which rapidly increased in size. These bubbles originated at the point of compression of the tubing.

TABLE III. CAROTID PERFUSION OF THE BRAIN IN 10 DOGS*

EXPERIMENT	SYSTEMIC BLOOD PRESSURE DURING PERFUSION† (MM. Hg)	DOG LUNG		PERFUSION FLOW (ML./KG./MIN.)	CAROTID TEMPERATURE (° C.)	CAROTID pO_2 (MM. Hg)	MEAN CAROTID PRESSURE (MM. Hg)	ΔP = T–P‡	FATE OF ANIMAL
		TEMPERATURE (° C.)	pO_2 (MM. Hg)						
1	100/ 62	35.0	582	13.2	35.8	638	135	–178	Survived
2	120/ 94	35.9	614	13.0	36.4	643	149	–239	Survived
3	100/ 72	35.8	635	16.5	36.3	625	129	–241	Survived
4	100/ 75	35.6	650	17.9	36.1	691	149	–183	Survived
5	164/118	35.0	667	14.9	35.6	690	138	–186	Survived
6	106/ 87	20.5	692	15.9	35.8	970	160	+76	Survived
7	90/ 70	20.1	639	15.7	35.3	1003	120	+158	Survived
8	108/ 80	20.6	650	17.4	36.0	965	117	+123	Died
9	86/ 57	20.5	704	16.5	36.0	825	126	–34	Died
10	116/ 74	20.6	658	12.5	35.8	1157	166	+267	Died

*Blood equilibrated with a gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide at 37° C. in the isolated dog-lung circuit was used in experiments 1 to 5. In experiments 6 to 10 the blood was equilibrated at 20° C. and then rewarmed to 36° C. before it entered the carotid circulation.

†Average of values recorded during perfusion.

‡ΔP = T-P, in which T = gas tension (carotid pO_2) and P = barometric pressure plus mean carotid pressure.

In Vivo Experiments.—

Details of the carotid-perfusion experiments are given in Table III. All of the dogs perfused with blood that had been equilibrated with a gas mixture

of 95 per cent oxygen and 5 per cent carbon dioxide at 36° C. survived and showed no evidence of cerebral damage. Of the 5 dogs perfused with blood that had been equilibrated with the gas mixture at 20° C. and then rewarmed to 36° C. just prior to being admitted to the carotid circulation, 3 failed to recover consciousness, and these animals died 16 to 18 hours postoperatively. No evidence of cerebral gas embolism or hemorrhage was found at postmortem examination.

COMMENT

When blood that had been equilibrated with oxygen at a low temperature (20° C.) was warmed, the tension of gas in the blood rose steadily until it surpassed the local absolute hydrostatic pressure. On the average, when the difference between tension and pressure was 80 mm. Hg, the steady formation of bubbles of gas was observed. This critical value of Δ P was associated in these experiments with an average temperature differential of 15° C. (21° to 36° C.). The converse experiment of altering hydrostatic pressure while the temperature was held constant yielded an average critical Δ P value of 150 mm. Hg. These findings are in accord with the formula $\Delta P = T - P$, by which Harvey's group[2] described the physical conditions that favored the release of gas from solution. In both types of experiment the total yield of gas was low, amounting to 0.5 to 1.0 ml. per hour at a flow rate of 0.1 L. per minute. This is about a thirtieth of the amount of gas that should have been evolved according to calculations of the pO_2 data, volume of blood, and rate of flow in the circuit.

For the entire series of experiments, the gas tension as measured by the pO_2 electrodes agreed within 5 per cent with the maximal possible gas tension calculated from analysis of the respiratory gas mixture. On three occasions, analysis of dissolved oxygen by the method of Van Slyke and Neill[3] yielded values that agreed within 10 per cent with those calculated from the oxygen tension as recorded by the Clarke electrodes. Two factors may be implicated in this discrepancy. The gas bubble evolved in the heating unit had to be detached from the surface of the heating tube and transported to the bubble trap, where it was collected and measured. Experiments with test tubes containing warmed blood and with tubes of blood exposed to a vacuum revealed a great tendency of small bubbles to cling to their surface of origin despite vigorous shaking and tapping. The surface area of the heat exchanger was 2,800 square centimeters. A layer of gas 0.05 mm. deep over half of this surface would yield a total volume of 7 ml. It is thus possible that the evolved gas bubbles remained adherent to the walls of the heat exchanger and that only a small proportion escaped in the form of free bubbles. Second, a measurable amount of oxygen was consumed by the pO_2 electrodes and by the blood. In the recirculation experiments in the isolated lesser circuit, this accounted for a major portion of the gas that theoretically should have been evolved but that in practice was not collected.

It is also possible, however, that the observed gas bubbles did not come from the blood[4] but represented instead the escape of gas nuclei trapped during the filling process and not removed despite circulation of the blood for 1 hour

through the apparatus. The experiments with the flasks and beads demonstrated the importance of these trapped micronuclei. The flasks with beads yielded gas bubbles more readily and in greater quantity than those without beads. Gas bubbles were also rapidly and readily evolved when fresh beads were added to a flask that did not contain beads.

In this respect, Harvey and co-workers[5] were unable to demonstrate gas nuclei in freshly drawn blood. However, animals exposed to compression of 3.5 atmospheres regularly showed bubbles within the blood vessels when decompressed to 1 atmosphere. They concluded that the gas nuclei were attached to or formed on the walls of the blood vessels, where, under proper conditions, they could grow and break loose as minute bubbles.

Whatever the source of the bubbles, these experiments demonstrated that measurable quantities of gas bubbles can be evolved from blood in an extracorporeal circuit under conditions in which gas tension is in excess of local hydrostatic pressure. In this regard, Fries and associates[6] demonstrated that the introduction of gas into the arterial circulation in the form of fine bubbles was as dangerous as the single injection of a similar volume of gas.

The experiments in which hydrostatic pressure was altered also indicated that under conditions of a positive value for Δ P, the additional stimulus of rapid local alterations in pressure results in a copious evolution of gas bubbles, in this case undoubtedly from the blood.

The results of the perfusion experiments were difficult to assess. The complete recovery of all 5 animals perfused with blood that had been equilibrated at 37° C. indicated that perfusion per se was well tolerated by the dog. The death of 3 of the 5 animals in the group perfused with blood that had been equilibrated at 20° C. may have been due to cerebral air embolism. However, no cerebral gas emboli could be demonstrated at necropsy, and the value of Δ P in the 2 surviving animals was as significant as that in the 3 animals that died. Bean,[7] in a review of the effects of oxygen at increased pressure, cited instances of involvement of the central nervous system on exposure to oxygen at a pressure of 3 atmospheres. The tension of oxygen in the blood perfusing the brains of the test animals was in excess of 760 mm. Hg. It was not known whether this level of gas tension per se would have an effect on the central nervous system.

SUMMARY

The rewarming in an extracorporeal perfusion system of blood that had been equilibrated with oxygen at a low temperature resulted in the release of gas bubbles when the tension of gas in the blood exceeded the local hydrostatic pressure. Bilateral carotid perfusion of the head with warmed blood (36° C.) that had previously been equilibrated with oxygen at 20° C. resulted in the death of 3 of 5 dogs.

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THE EXTERNAL CARDIAC PACEMAKER: ADJUNCT IN INCREASING THE VOLUME OF AVAILABLE BLOOD FROM DONOR ANIMALS, WITH ESPECIAL REFERENCE TO EXTRACORPOREAL BYPASS

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CARDIOVASCULAR research, utilizing the various pump-oxygenators, has become an important part of most surgical training programs. With increasing utilization of this equipment and with the introduction of heat exchangers and other new components to existing systems, priming volumes for this equipment have increased. From the economic as well as the humane aspect, efficient techniques of obtaining and utilizing these volumes must be practiced.

It is our purpose briefly to discuss a donor collection method in the dog and to emphasize the value of the external cardiac pacemaker* as an adjunct in more complete donor exsanguination.

METHOD

The donor is weighed to estimate the amount of blood theoretically available. Initial sedation is accomplished using intravenous diphenhydramine, 2 mg. per kilogram of body weight, then thiopental sodium, 2 per cent solution, is given intravenously to anesthetize the donor for a femoral arteriotomy. The donor is placed in the supine position, the inner thigh is shaved, and arteriotomy quickly accomplished. The appropriate sized arterial catheter is threaded high into the aorta and tied into place.

The catheter is opened to allow blood collection into 500 c.c. receptacles containing 20 mg. of heparin. The two electrodes of the external cardiac pacemaker are now secured by a rubber strap in the sixth intercostal space of the left lateral thorax. Mechanical ventilation through an endotracheal tube is started.

As cardiac output fails, the external cardiac pacemaker is started at a rate of 100 beats per minute with an initial amplitude of 90 volts, gradually increasing to 120 volts. This is continued until donor output terminates.

RESULTS

Powers and co-workers[1] observed the average weight of the blood in a dog to be 11.9 per cent of the total body weight. This figure has been thought to be closer to 10.5 per cent by others.[2] Thus, we may estimate the intravascular volume to be approximately 105 c.c. per kilogram of body weight. The dog

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*Electrodyne Transistor Pacemaker, Model TR-3. Electrodyne Co., Inc., Norwood, Mass.

heart cannot maintain circulation when the blood volume is reduced below two thirds of the normal amount.[2] Therefore we have established a figure of 70 c.c. per kilogram of body weight as being available for collection purposes under normal circumstances. Values below this figure represent ineffective utilization of donors.

Using the external cardiac pacemaker, volumes consistently above 70 c.c. per kilogram have been obtained in healthy dogs; blood volumes have averaged over 3 per cent above the estimated volumes in all dogs, an occasional donor producing as much as 10 per cent above the estimated available volume (Table I). Blood volumes have averaged over 5 per cent above estimated available volumes in healthy animals. Donors who are recovering from previous surgical procedures or who are in poor health commonly have decreased blood volumes.

TABLE I. TYPICAL VOLUMES OBTAINED FROM 10 RECENT CONSECUTIVE DONORS

TOTAL BODY WEIGHT (KG.)	ESTIMATED DONOR VOLUME	OBTAINED VOLUME	GAIN BY PACEMAKER (C.C.)	CUBIC CENTIMETERS PER KILOGRAM OF BODY WEIGHT
1. 15.0	1,050	1,180	130	78.7
2. 20.1	1,407	1,510	103	75.1
3. 33.7	2,359	2,350	—	69.7*
4. 31.7	2,219	2,410	191	77.5
5. 21.1	1,477	1,480	3	70.1
6. 20.2	1,414	1,500	86	74.2
7. 32.4	2,268	2,140	—	66.0*
8. 20.0	1,400	1,410	10	70.5
9. 32.5	2,275	2,275	0	70.0
10. 50.2	3,514	3,650	136	72.7
			Average all animals	72.5
			Average healthy animals	73.6

*Recovered from recent surgical procedure.

The pacemaker appears to increase donor volumes by two means. First, it facilitates mobilization of pooled peripheral blood through contraction of skeletal muscles. Second, it accentuates ineffective myocardial contraction at the termination of donor output when the anoxic myocardium will not respond effectively to normal conduction mechanisms. Visualized on the electrocardiogram, during exsanguination, the heart action is little affected by the pacemaker until a falling systemic pressure no longer maintains coronary circulation and arrhythmia develops. The pacemaker transforms the arrhythmia into a regular rhythm which persists even after the donor blood output ceases.

DISCUSSION OF TECHNIQUES

To obviate untoward response by the perfused recipient to agents in donor blood, the collection of this blood without the use of sedatives or analgesics would be desirable. This becomes of prime consideration when either physiologic values or responses to cardiovascular procedures per se are being measured. The presence of these agents may markedly change the response of the recipient to a specific drug or procedure and thus vitiate all data. Such a technique of collection requires several assistants because of difficulties in handling the donor.

Thus, a barbiturate is commonly given intravenously to produce a light stage of anesthesia. Controlling the amount of barbiturate is important for two reasons: (1) depressed donors seldom yield anticipated volumes; (2) a donor may require 25 mg. per kilogram of thiopental sodium for exsanguination purposes whereas only 15 mg. per kilogram of this drug may be adequate for the surgical procedure in a particular animal. Pentobarbital sodium and thiopental sodium have been used for donor anesthesia but the latter is preferred because of its shorter duration of action.

Mechanical respiration, given through endotracheal intubation, is beneficial when breathing becomes irregular or ineffective; it also facilitates mobilization of blood which would pool in the pulmonary vascular bed during the diminished respiratory phase. Antihistamines, particularly diphenhydramine, 2 mg. per kilogram, are given intravenously prior to the barbiturate. This use is based on recent experimental evidence demonstrating a decrease in anaphylactoid shock in blood exchange after the use of diphenhydramine.[3, 4] In addition, the potentiation of the thiopental sodium by diphenhydramine reduces the required anesthetic dose of the thiopental.

SUMMARY

In securing blood from donor animals to fill the extracorporeal pump-oxygenator, the external cardiac pacemaker has commonly increased the total blood yield. This has decreased the number of animals sacrificed as donors and allowed for a larger surplus of blood during individual bypass procedures.

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OPERATION FOR PECTUS EXCAVATUM USING STAINLESS STEEL WIRE MESH

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In the operation for pectus excavatum, one of the difficult aspects of the procedure is to maintain the elevation of the sternum at the completion of the dissection. There have been many satisfactory methods proposed, and still another is being reported for consideration—one that offers the advantages of simplicity of application, permanence of support, and effective elevation of the distal portion of the sternum. For clarity the entire technique of the procedure is illustrated (Figs. 1, 2, and 3), but, in general, the operation sequences are the same as described by Brown, Ravitch, and Lester. After the dissection of the sternum from the anterior mediastinum and the wedge-shaped osteotomy permits elevation of the gladiolus, a sling of stainless steel wire mesh is placed over the ribs and under the sternum, holding it up tautly. Two or three mattress sutures placed through the mesh into the periosteum of the ribs is all that is necessary to fix the stainless steel mesh in place.

The remainder of the closure is simple, with approximation of the muscle, fascia, and skin in their respective planes with usual suture material.

No. 10 Robinson catheters, with additional perforations, are placed prior to closure. The catheters are brought out through stab wounds and attached later to low pressure suction and removed on the fourth postoperative day.

Illustrative Case.—D. B. was referred because of marked thoracic deformity and complaints of shortness of breath and inability to gain weight. Operation was performed, using the method just described, on Aug. 3, 1959. The postoperative course was completely uneventful and 10 months later the patient is free from symptoms of shortness of breath, has gained 20 pounds, and feels better than ever before. At the present time the thorax is completely stable and the elevation of the sternum is perfectly maintained (Fig. 4, *A* and *B*).

SUMMARY

An additional method of stabilizing the elevated sternum during operation for pectus excavatum using stainless steel wire mesh is described, together with minor refinements of the surgical procedure.

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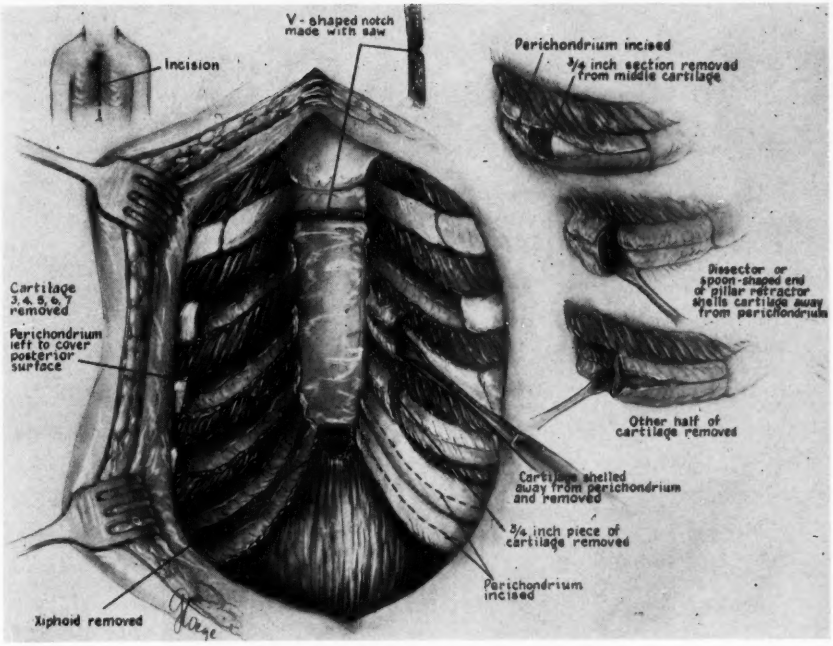

V - shaped notch made with saw
Incision
Perichondrium incised
3/4 inch section removed from middle cartilage
Dissector or spoon-shaped end of pillar retractor shells cartilage away from perichondrium
Cartilage 3, 4, 5, 6, 7 removed
Perichondrium left to cover posterior surface
Other half of cartilage removed
Cartilage shelled away from perichondrium and removed
3/4 inch piece of cartilage removed
Perichondrium incised
Xiphoid removed

Fig. 1.

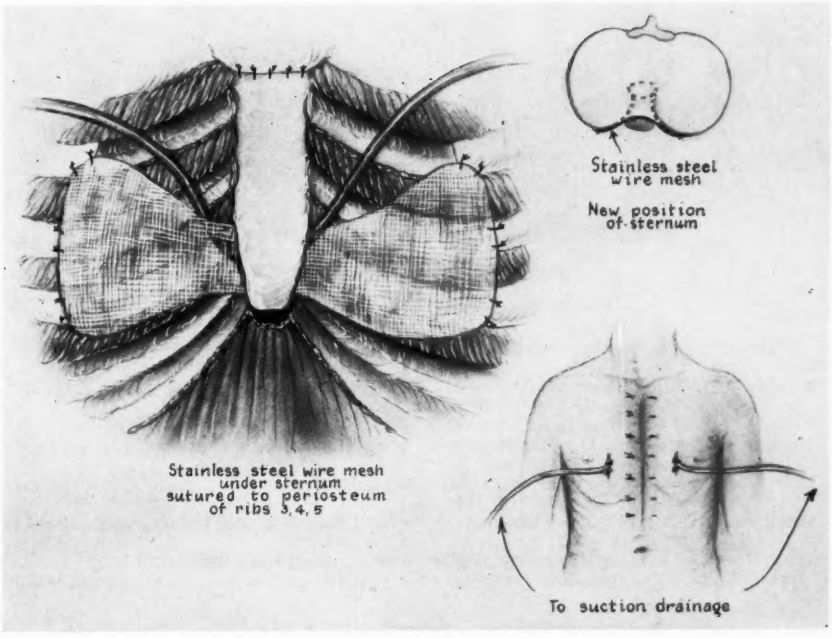

Stainless steel wire mesh
New position of sternum
Stainless steel wire mesh under sternum sutured to periosteum of ribs 3, 4, 5
To suction drainage

Fig. 2.

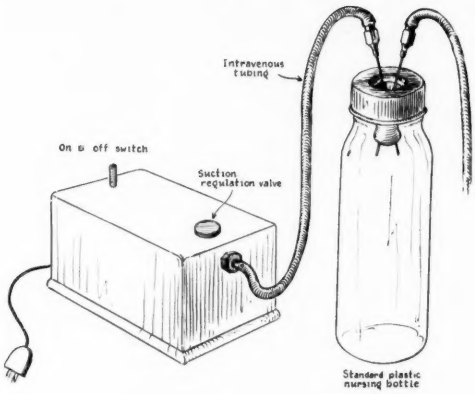
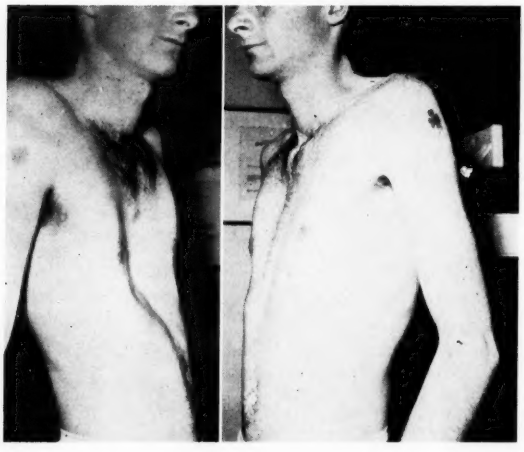


Fig. 3.



A. *B.*

Fig. 4.

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Members Deceased

FRANK S. DOLLEY
ROBERT P. GLOVER
CHEVALIER L. JACKSON
R. STARR LAMPSON
WILLIAM LERCHE
ROBERT T. MILLER, JR.

ANNUAL MEETING NOTES

The Forty-first Annual Meeting of The American Association for Thoracic Surgery was held in Philadelphia, Pennsylvania, April 24, 25, 26, 1961. There were 1,095 physicians who registered for the scientific sessions. In addition there were 155 wives present. Foreign guests and visitors were again numerous and included, this time, a representative from the U.S.S.R. The special guest, Professor A. L. d'Abreu, of Birmingham, England, was accorded Honorary Membership.

The following changes in membership status were approved after due process:

The resignations of two members were accepted with regret.

The following Active members were elevated to Senior status:

Frank Bortone
Paul D. Crimm
Herbert W. Schmidt
Willard Van Hazel
Warriner Woodruff

The following Associate members were elevated to Active membership:

Paul C. Adkins
Jay L. Ankeney
Raymond J. Barrett
Hector W. Benoit, Jr.
James W. Brooks
Gilbert S. Campbell
R Adams Cowley
Thomas B. Ferguson
Charles W. Findlay, Jr.
Joseph M. Ford
Allen E. Greer
Edward J. Jahnke, Jr.
Thomas N. P. Johns
Frank R. Johnston
James B. Littlefield
Irving M. Madoff
James V. Maloney, Jr.
Dwight C. McGoon
Charles V. Meckstroth
Joe D. Morris
William T. Mustard
Russell M. Nelson
David V. Pecora
Rex Beach Perkins
Howard D. Sirak
Timothy Takaro
Joseph J. Timmes
Earle W. Wilkins, Jr.
William Glenn Young, Jr.

The following candidates were elected to Associate membership:

Elmore M. Aronstam, Denver, Colo.
Wilfred G. Bigelow, Toronto, Ontario
Morley Cohen, Winnipeg, Manitoba
A. Robert Cordell, Winston-Salem, N. C.
W. Sterling Edwards, Birmingham, Ala.
Charles Fineberg, Havertown, Pa.

Alfred S. Frobese, Bryn Mawr, Pa.
Joseph W. Gilbert, Jr., Bethesda, Md.
George J. Haupt, Philadelphia, Pa.
George R. Holswade, New York, N. Y.
John M. Howard, Philadelphia, Pa.
Charles H. Lasley, Clearwater, Fla.
Montague S. Lawrence, Iowa City, Iowa
Robert S. Litwak, Miami, Fla.
George J. Magovern, Pittsburgh, Pa.
George E. Miller, Calgary, Alberta
George C. Morris, Jr., Houston, Tex.
JD Mortensen, Salt Lake City, Utah
Alton Ochsner, Jr., New Orleans, La.
Laurence M. Rivkin, San Francisco, Calif.
Norman E. Shumway, Palo Alto, Calif.
Albert Starr, Portland, Ore.
Sam E. Stephenson, Jr., Nashville, Tenn.
Harold Stern, New Haven, Conn.
Wendell B. Thrower, Charleston, S. C.
Myron W. Wheat, Jr., Gainesville, Fla.
Walter A. Wichern, Jr., New York, N. Y.